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BULLETIN OF
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MAY 1942

SOME CHEMICAL CHANGES IN THE MYOCARDIUM ACCOMPANYING HEART FAILURE*

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THE normal function of the heart is dependent upon a recurrent series of beautifully coördinated physical and chemical processes. Obviously a break anywhere in this chain of processes affects the action of the heart as a whole. Much attention has been given to the pathology of the heart and its effect, not only upon the circulation of the blood, but also upon the blood supply and nutrition of the heart itself. Two of my Cleveland colleagues[1, 2] have recently addressed the Academy upon topics dealing with this general subject. It is evident that the normal function of the heart cannot be maintained without an adequate blood supply, to furnish food materials, including oxygen, for the energy of the heart's action. It is equally evident that the heart is dependent upon a properly functioning chemical mechanism by which this material can be converted into mechanical energy. It is this last phase of the subject that I wish to discuss.

With the discovery of phosphocreatine by Fiske and Subbarow[3] in

* Presented at a joint meeting of the New York Heart Association and the Section on Medicine of The New York Academy of Medicine, January 20, 1942.

1927, and the subsequent discovery of adenosinetriphosphate, our theories regarding the energetics of muscular activity have been entirely changed. Without entering into a theoretical discussion, it would appear that compounds of phosphorus, phosphocreatine and adenosinetriphosphate in particular, are intermediaries in the transfer of chemical energy to the mechanical energy of the heart beat. It seems probable that these organic phosphoric acid compounds exist as potassium salts,[4] and would thus account for most of the intracellular potassium. If the above premises are correct, the concentration of these compounds in the myocardium should serve as an index of the potential capacity of the heart for work.

Phosphocreatine is such a labile compound that it is impossible to determine it in the human heart obtained at autopsy. However, variations in creatine are probably equally significant. It should therefore be of interest to study the changes which occur in the creatine, purine nitrogen, phosphorus and potassium of the myocardium in disease. In addition, adequate evaluation of these data might be difficult without information on the water, sodium chloride, lipid and collagen content of the tissue.

With this background a series of studies on human hearts obtained at autopsy was begun in our laboratory in coöperation with the Department of Pathology more than ten years ago. Any success that may have been achieved has been due largely to the work of Linegar and Mangun of our department, to the coöperation of Seecof, Frost, Reichle and Strauss of the Department of Pathology, and to the financial assistance of the Josiah Macy, Jr. Foundation.

Although we were apparently the first in this country to undertake studies on the heart involving creatine[5] we were slow in reporting our findings, and almost simultaneously and independently Cowan[6] in Iowa City, and shortly afterwards Herrmann and his co-workers[7] in Galveston reported creatine observations on the heart in agreement with our own. Herrmann in particular has vigorously attacked the problem, employing both animal and human material.

About the time our studies were undertaken the Vanderbilt University medical group attacked the problem of congestive heart failure from the standpoint of potassium. Calhoun, Cullen, Clarke and Harrison[8] concluded one of their early papers with the statement: "It is believed that overwork causes loss of potassium from heart muscle and

TABLE I

AVERAGE DATA ON HEARTS OF THIRTEEN NORMAL HUMAN SUBJECTS
(mg. per 100 gm. of wet tissue)

Constituent	*Left ventricle*	*Right ventricle*	*Voluntary muscle*
Creatine	203	165	443
Phosphorus	194	160	201
Potassium	285	219	328
Water	80.8	82.3	76.2
Fat	0.35	1.28	1.68

that this loss is one of the predisposing factors to cardiac fatigue and failure." This statement is interesting and apparently correct, but appeared to us to be only part of a much larger chemical picture, involving creatine, phosphoric acid and adenosinetriphosphate.

Several brief statements may help in orientation. Creatine is present in heart muscle in about half the concentration it attains in skeletal muscle. Phosphocreatine has been reported by various investigators as present in concentrations from one-tenth to one-third that of skeletal muscle. Its lower concentration in heart muscle than in skeletal muscle cannot be attributed to a difference in the amount of the intracellular phase, since there is a sharp decrease in the ratio of creatine to potassium. The distribution of phosphorus compounds is likewise greatly different from that of skeletal muscle. While the total phosphorus of the heart is about the same as that of skeletal muscle, a much greater part is present in the acid-insoluble fraction, most of which is phospholipid. The acid-soluble fraction is accordingly less, and this difference may be traced largely to the lower phosphocreatine content of the heart.

When we began our study we were inclined to believe that the averages for our relatively large pathological series, covering a considerable range of values, would furnish figures not far from normal and adequate controls. This was nearly correct in the case of the myocardium, but not in the case of the voluntary muscle. If our theories regarding the function of phosphocreatine are correct, the creatine level in the myocardium must be reasonably maintained if heart failure is to be prevented. To secure more adequate control data hearts from 13 indi-

viduals dying accidental deaths were analyzed.[9] Average data are presented in Table I. As will be noted the creatine, phosphorus and potassium are appreciably higher in the left than in the right ventricle. In the beginning we were inclined to attach special significance to this.[5] It will be observed, however, that the water and fat are appreciably higher in the right ventricle. This also appears to be true for the connective tissue content.[10] When allowance is made for the difference in the extracellular water, the fat and connective tissue, the difference between the ventricles is relatively small.

At this point it may be well to ask if the changes observed in the wet muscle of pathological hearts may not be due primarily to changes in water, connective tissue and fat. Wilkins and Cullen[11] have shown that in persons dying from congestive heart failure there is an increase in the water content of both ventricles, but especially the right ventricle. As might be expected this increase in water is accompanied by an increase in the sodium content, obviously in the form of sodium chloride. Recalculation of our figures on the basis of water and fat free tissue did not eliminate the very definite changes which occur in heart failure. On this account we have continued to record our findings on the basis of the wet tissue, since this is the condition in which the heart functions.

Since creatine appears to us to loom large in point of quantity and significance in heart failure, it will be well to call attention to several outside factors which exert some influence on the creatine content of the myocardium. Probably the most important of these are factors affecting the metabolism of creatine and the elimination of creatinine, which are reflected in the creatine content of voluntary muscle. Whereas the creatine content of voluntary muscle averages about 400 mg. per 100 gm. of fresh tissue in miscellaneous pathological conditions, it is definitely higher in strictly normal individuals, namely 443 mg. In uremia and fevers the creatine values tend to be elevated and range from 400 to 560 mg., while in such conditions as carcinoma and diabetes the concentration is definitely lowered—may reach 300 mg. The retention of creatinine no doubt accounts for the high creatine values observed in voluntary muscle in uremia. Hyperthermia is known to greatly increase the urinary excretion of creatinine and the relatively high creatine values found in fevers are probably explained in part at least by the whipping-up of creatine-creatinine metabolism. On the other

hand, the very low values found in diabetes may find explanation in the disturbance of carbohydrate metabolism.

In studying our data[12] on the creatine content of the left and right ventricle in comparison with the voluntary muscle, it was observed that the high values for the creatine of voluntary muscle in uremia and pneumonia were accompanied by correspondingly high values in the left ventricle, and in the right ventricle in uremia, but not in pneumonia. In diabetes, on the other hand, the creatine of the left ventricle is only slightly lowered, despite the marked fall in the voluntary muscle, suggesting that the creatine level of the heart muscle must be maintained if the heart is to function.

To secure further information on the influence on the myocardium of factors which elevate the creatine content of voluntary muscle, the data[12] were rearranged and grouped on the basis of the creatine content of voluntary muscle. It was found that as long as the creatine concentration of the voluntary muscle did not exceed about 425 mg. there was no elevating influence on the creatine content of the myocardium. When it exceeded this level, however, there was a definitely elevating effect on the creatine concentration of the left ventricle, although the values in the right ventricle remained essentially normal.

Cardiac Hypertrophy. The question of the effect of cardiac hypertrophy upon the chemical composition of the human heart is of importance both as a phenomenon in itself and in relation to myocardial failure. It would appear that cardiac hypertrophy is intimately associated with failure and may possibly be the principal factor in bringing about an eventual breakdown in the metabolic transfer between the blood and muscle required to keep pace with the increased demands upon the energy output. Wearn and his co-workers[2] have shown that as a result of the increase in diameter of the muscle fibers in hypertrophy there is a decrease in the number of capillaries per square millimeter of heart muscle. This ultimately leads to a considerable increase in the radial distance the metabolites must diffuse from each capillary, a situation which may conceivably lead to decreased nutrition and anoxia of the muscle fibers.

It is difficult to obtain entirely satisfactory information on the effect of hypertrophy on the chemical composition of the human heart because of the variability of the findings and the influence of other factors. Cowan[6] observed that in hearts with hypertrophy the average

TABLE II

THE RELATION BETWEEN HEART WEIGHTS AND CONCENTRATION OF CREATINE, PHOSPHORUS AND POTASSIUM
(EXCLUSIVE OF NITROGEN RETENTION CASES)
(mg. per 100 gm. of wet tissue)

Group	*Number of Cases*	*Weight of Hearts (gm.)*	LEFT VENTRICLE			RIGHT VENTRICLE		
			Creatine	*P*	*K*	*Creatine*	*P*	*K*
I	4	200-230	213	201	299	182	183	242
II	5	250-275	244	195	306	191	162	241
III	7	300-350	210	189	269	179	148	212
IV	9	375-450	196	181	271	152	145	195
V	7	450-530	177	178	265	129	141	192
VI	8	550-650	152	168	232	126	142	191
VII	4	650-825	140	184	213	110	140	172
Normals	13	275-500	203	194	285	165	160	219

creatine concentration was slightly higher than in hearts without hypertrophy, but did not regard the difference as significant. In experimental studies in the rabbit Herrmann and his co-workers[13] found that slight hypertrophy resulted in a definite rise in the creatine concentration which was somewhat more marked in the left than in the right ventricle. With more definite hypertrophy the creatine concentration dropped to considerably below the normal level in the left ventricle and to about the normal level in the right ventricle. It is of some interest that digitalized hearts showed a slight increase in creatine concentration.

In work carried out on human and animal hearts in our laboratory we have persistently noted a tendency toward higher creatine, phosphorus and potassium values with increases in heart weight. These differences, however, have been relatively small and of such magnitude as might be expected from variations in the amount of the intracellular phase in the myocardium. In an effort to ascertain the relation between heart weight and creatine content throughout the normal and pathological range we charted the data on 195 cases arranged according to heart weight.[14] The findings may be summarized with the statement that at birth there is little difference in the creatine concentration of

TABLE III

AVERAGE CREATINE, PHOSPHORUS AND POTASSIUM CONCENTRATIONS IN CARDIAC MUSCLE IN MYOCARDIAL INSUFFICIENCY, COMPARED WITH OTHER PATHOLOGICAL CONDITIONS AND THE NORMAL

(mg. per 100 gm. of wet tissue)

Condition	*No. of Cases*	LEFT VENTRICLE			RIGHT VENTRICLE		
		Creatine	*P*	*K*	*Creatine*	*P*	*K*
Myocardial insufficiency	17	146	169	232	112	135	178
Miscellaneous cardiac involvement	20	190	185	259	149	148	195
Cor pulmonale	4	217	186	271	136	132	166
Diabetes mellitus	3	200	197	272	126	144	194
Uremia without heart failure	11	246	199	286	182	153	205
Normals	13	203	194	285	165	160	219

the muscle of the two ventricles. After birth the creatine concentration rises rapidly in the left ventricle, although the rise in the right ventricle is slight. Creatine reaches a maximum in the left ventricle in the 50 to 150 gm. hearts, in the right ventricle in the 150 to 250 gm. hearts, maintains its highest level up to 350 gm., and then begins to fall, reaching its lowest level in the group of adult hearts weighing over 650 gm.

To rule out a factor which, as already noted, exerts a pronounced elevating influence on the level of creatine in the heart, namely nitrogen retention with its accompanying retention of creatinine and creatine, a table was prepared from data on 44 autopsy cases covering the range of heart weights but excluding all cases with nitrogen retention. It will be observed in Table II that with the first increments in heart weight there is a quite definite elevation not only of creatine in both ventricles but also of phosphorus and potassium. However, with further increments in heart weight all the values begin to fall and decline with each increment in heart weight, the final values being 20 to 35 per cent below the normal. Obviously the incidence of heart failure increases progressively with each increment of heart weight. It should be noted, however, that relatively high creatine values were frequently observed throughout the range of heart weights, indicating that hypertrophy itself does not necessarily limit the saturation level of the muscle.

Myocardial Insufficiency. The chemical changes which occur in the

myocardium in heart failure appear especially significant. Average data on 17 cases[15] of myocardial failure are recorded in Table III, and similar data on cases classified as miscellaneous cardiac involvement, cor pulmonale, diabetes mellitus, uremia and normals for comparison. Only those patients whose condition was clinically diagnosed as myocardial insufficiency and who showed evidence of progressive decompensation with hyperemia of the internal organs and edema of the extremities, were included in this group of seventeen cases. Patients with less distinct signs of myocardial insufficiency, as well as those with nitrogen retention, were classified separately. As will be observed the average concentrations of creatine, phosphorus and potassium were decreased in both ventricles of the heart. In every case the creatine content of the left ventricle was below the normal level, varying from 16 to 52 per cent below the normal. The concentration of phosphorus was likewise lowered, but to a less degree, in all but 2 of the individual cases. The potassium also decreased in all but 2 cases, the average percentage decrease being somewhat more than that for phosphorus and less than that for creatine. Similarly lowered values are recorded for the right ventricle. It should probably be noted that in this series of cases with myocardial failure there was also a definite reduction in the creatine content of the voluntary muscle (average of 349 mg.), probably due in part to long enforced inactivity.

In attempting to interpret the losses in creatine, phosphorus and potassium which occurred in these cases of myocardial insufficiency, it appeared helpful to consider not only the percentage loss, but also the loss in relation to the molecule, dipotassium phosphocreatine. If the observed decreases were due chiefly to dilution of the active muscle tissue with water, fat or connective tissue, one might anticipate that the whole of the creatine, phosphorus and potassium would be affected. The net result would be that a decrease of 10 per cent, for example, in the creatine would be accompanied by a decrease of 10 per cent in the phosphorus and potassium. On the other hand, if the changes observed were due largely to a breakdown of the phosphocreatine mechanism, only that part of the phosphorus and potassium directly associated with the creatine might be expected to be lost.

When the data were calculated in terms of percentage decrease in the three constituents, and in terms of loss of millimoles per kilogram it was apparent that tissue dilution was not the important factor in-

TABLE IV

AVERAGE ADENINE (CALCULATED FROM OXY-PURINE NITROGEN), CREATINE AND TOTAL ACID-SOLUBLE PHOSPHORUS CONTENT OF HUMAN CARDIAC MUSCLE IN HEART FAILURE AND OTHER CONDITIONS
(mg. per 100 gm. of wet tissue)

	No. of Cases	LEFT VENTRICLE			RIGHT VENTRICLE		
		Adenine	*Creatine*	*T A S P*	*Adenine*	*Creatine*	*T A S P*
Entire Series	24	86	205	106	54	152	74
Heart Failure	6	72	161	91	54	128	67
Tuberculosis	5	87	225	117	56	162	78
Pneumonia	8	90	222	110	48	160	75
Miscellaneous	5	91	211	107	63	161	78

volved, since there was no correlation between the percentage decreases of the three constituents in either ventricle. Calculations were then made on the assumption of the loss of the components of dipotassium phosphocreatine. Taking the loss of 4 mols of creatine as the standard of reference, one would expect a loss of 4 mols of phosphorus and 8 mols of potassium. The actual loss of phosphorus and potassium was found to exceed that of creatine.[15] This fact is suggestive of a loss of adenosinetriphosphate, which would be in harmony with the findings of Burns and Cruickshank[16] that this compound may break down in the heart under a variety of experimental conditions.

Recently we[17] have put this question to experimental test as shown in Table IV. In a series of twenty-four human hearts, including six cases of congestive heart failure, we have carried out purine determinations in addition to determinations of creatine and total acid-soluble phosphorus. The nitrogen of the purines convertible to oxypurines was determined, and from this adenine was calculated. It will be observed that in heart failure the left ventricle shows a decrease in this purine fraction along with the decrease in creatine and total acid-soluble phosphorus. This fall does not appear to occur in the right ventricle. It should perhaps be noted that there does appear to be a drop in the adenine of the right heart in pneumonia. From the above it would seem that adenosinetriphosphate probably accounts for the major part of the phosphorus and potassium loss not accounted for by the creatine. There-

fore it does not appear probable that extensive changes occur in organic compounds of phosphorus other than phosphocreatine and adenosinetriphosphate.

Our series of cases has included only one case of coronary failure (thrombosis). Samples taken from areas that were not infarcted gave values within the normal range. Herrmann and Decherd[18] have made creatine determinations in a number of such cases, cases that were presumably less acute than our single case, and observed a marked reduction of creatine in the infarcted areas, and a considerable reduction in the uninfarcted areas. In our cases of miscellaneous cardiac involvement (Table III) the average values are only moderately reduced. Data are also included in Table III on 4 cases of right-sided heart failure (cor pulmonale), showing comparatively low values in the right ventricle. While the heart fails as a unit it is evident that the right ventricle may show chemical evidence of failure without similar changes occurring in the left ventricle. The table likewise includes data on 3 cases of diabetes mellitus. Here too the findings for the left ventricle are essentially normal, but in the right ventricle the concentrations of all three constituents, especially the creatine, are reduced. It is interesting to note that in uremia essentially all the values for creatine, phosphorus and potassium are above normal, or normal, in the left ventricle and right ventricle (also in the voluntary muscle), although the greatest increase is in the creatine. In our earlier study[12] which included a slightly smaller number of cases we observed that in uremia without heart failure the creatine values were markedly increased, whereas in uremia with heart failure they were reduced. At the time we suggested that the high creatine values in uremia without heart failure might explain why the heart did not fail in these cases. This is an interesting question which requires further study. The fact that in uremia there is a tendency towards elevation of phosphorus and potassium as well as creatine suggests the possibility that the extra creatine may be retained as the potassium salt of phosphocreatine. Whether or not this might exert a beneficial effect on the heart by increasing the energy and base reserve of the myocardium is an interesting speculation.

It is obvious that while the most important fundamental chemical changes occurring in the myocardium in heart failure are probably indicated by the average values recorded in the tables and already discussed, many interesting and important points regarding the individual cases are

covered up by this procedure. For example, in many instances the changes are more pronounced in one ventricle than in the other. Comment on this would require discussion of individual cases, or small groups of cases, which is beyond the scope of the present paper.

Discussion. It is interesting to note that the chemical approach to the problem of heart failure was first attacked with the determination of creatine in the myocardium by Constabel[19] in 1921 and that to date no other substance has been conclusively shown to be as greatly affected by myocardial insufficiency. Since the pioneer investigation of Constabel, carried out on only a few hearts, it has become more and more apparent that this substance is decreased in the failing heart. On this point all investigators in the field are agreed. The underlying cause of the decrease in creatine content of the myocardium, however, has sometimes been challenged.

It has been suggested that the decrease in creatine is due to anatomical changes in the muscle, to hypertrophy of noncreatine containing parts of the cells, and to injury of the cell membranes, permitting the diffusion of creatine out of the cells.

Let us examine the evidence brought forward to show that the decrease in creatine is without significance. Determinations of the water content by various investigators have demonstrated that only a small fraction of the drop in creatine concentration can be assigned to this factor. While there is usually a small increase in the water content of the failing heart, and occasionally a significant increase, this factor is negligible with respect to creatine, although it may be of importance in itself as a factor interfering with the metabolic activity of the myocardium. The possibility that anatomical alterations, such as fatty infiltration and increases in connective tissue, may be responsible have been discounted by workers who have examined the heart histologically in conjunction with their analyses. At this point it is interesting to note that Hastings and his co-workers,[20] in experimental studies on the heart, have obtained quantitative evidence of chemical alterations in the absence of demonstrable histological changes. In our studies we have determined the water, fat and collagen content in a limited number of cases and have been unable to demonstrate any serious alterations in the values for creatine, phosphorus, and potassium after correction for these factors. Occasionally the fat and collagen content have been found to be increased particularly in the right ventricle, but these alterations in

individual cases exert a negligible effect upon the group of cases studied in this manner. It would, nevertheless, be highly desirable to have more extensive studies conducted which included the collagen content of the heart, especially in relation to age, hypertrophy, and infarction. Blumgart and his associates[21] have recently measured myocardial fibrosis by chemically determining the collagen content and found that all cases having abnormally high collagen values, showed either marked coronary sclerosis with occlusions, or hypertrophy.

The possibility that injury of the cell membrane is responsible for the loss of creatine hardly seems credible. There is ample evidence in the literature to indicate that creatine may be taken up by muscle as well as released by it.

The final alternative then is that the loss of creatine is due to chemical events within the cell, an inability to maintain the creatine in the nondiffusible form of phosphocreatine. This loss in creatine is accompanied by, and apparently correlated with, losses in phosphorus, potassium and adenosinetriphosphate.

At the present time it would not appear that our knowledge of the chemistry of the heart can be readily applied to improve the treatment of myocardial insufficiency. Nevertheless, there is a definite relationship between the chemical events which occur in the heart and the therapy applied to congestive failure. The ability of the heart at any given time to contract will depend upon the summated result of all the factors that contribute this energy versus all those factors which tend to dissipate, consume, or interfere with the production. So far as we know at the present time, phosphocreatine and adenosinetriphosphate are the two substances most closely associated with the final stages in the transfer of chemical energy to mechanical energy. To build up this final reaction to its highest level, we are, therefore, interested in attaining two objectives: increasing the rate at which energy is made available and decreasing the demands upon the system. In other words, we are interested in maintaining the optimum concentration of phosphocreatine and adenosinetriphosphate and yet having them supply energy at an adequate rate, with the least possible dissipation. In the compensated heart the relative rates of the reactions centering about the phosphocreatine-adenosinetriphosphate system are such that energy input and energy expenditure are in equilibrium at a point where adequate amounts of phosphocreatine and adenosinetriphosphate are present.

At this point it is of interest to note that the chemical changes in phosphocreatine and adenosinetriphosphate, by which mechanical energy is released probably play a very important role in another connection, namely in the induction of the electric currents in the heart muscle which are recorded by the electrocardiograph. When the contractility and conductivity of the muscle cells are impaired, for example by infarction, with consequent loss of phosphocreatine and adenosinetriphosphate, characteristic electrocardiographic changes occur which can be related to certain areas of the heart.

Most of the established methods of treating heart failure are probably effective largely because they decrease the demands upon the heart, thus permitting the energy input to keep abreast of the expenditure. The most outstanding of these types of therapy are rest, digitalis, and the removal of edema through regulation of the water and electrolyte balance. The latter may exert some direct beneficial effect upon the myocardium by removing edema fluid from that tissue, thereby accelerating the metabolic transfer. The possible direct action of digitalis upon the heart muscle still remains a subject of controversy.

While it is generally believed that the fundamental causes of decompensation may be attributed to increased demands upon the heart to perform work and decreased ability to perform such work as a result of disturbances in the coronary circulation, these considerations should by no means limit the possibilities of bolstering the heart action by measures directly affecting the myocardium. Attempts have been made to increase the creatine content of the heart experimentally or to prevent its loss by the addition of creatine to perfusing fluids, but these measures thus far have met with little success. Similar attempts to increase the intracellular electrolytes of patients by feeding dipotassium phosphate have likewise met with failure. Kalter[22] administered glycine, a creatine precursor, to patients with decompensated heart disease and reported several cases in which it apparently exerted a beneficial effect and was enthusiastic about the possibilities of this therapy. Herrmann and Decherd[18] have also reported experiments in which the administration of glycine appeared to have beneficial effects. However, such studies are difficult to control, and one should be cautious in making interpretations.

Summary. We may conclude then that there is reasonably good evidence, direct and circumstantial, that phosphocreatine and adeno-

sinetriphosphate, as potassium salts, play an essential role in muscular activity, or more specifically are vital agents in the transfer of chemical to mechanical energy for muscular work. The chemical findings just reported on human heart muscle are in harmony with this hypothesis. Essentially normal values have been established for creatine, phosphorus, potassium and adenine in the muscle of the left and right ventricle. In the very early stages of cardiac hypertrophy there appears to be an increase in the concentration of these constituents, but with further hypertrophy all the values begin to fall and reach their lowest levels with extreme cardiac hypertrophy and heart failure. While it has not been definitely established that heart failure is due to the decreased concentration of these apparently vital constituents, or disproven that these changes merely accompany heart failure, the evidence appears to support the former view. Although the chemical observations reported have not as yet led to any established advance in therapy, still such data should materially aid in interpreting some of the clinical findings in diseases of the heart and in rationalizing treatment. It is hoped that the few observations reported may be the forerunners of more important biochemical studies on the heart.

REFERENCES

1. Wiggers, C. J. Basic hemodynamic principles essential to interpretation of cardiovascular disorders, *Bull. New York Acad. Med.*, 1942, *18:*3.
2. Wearn, J. T. Morphological and functional alterations of the coronary circulation, *Bull. New York Acad. Med.*, 1941, *17:*754.
3. Fiske, C. H. and Subbarow, Y. Nature of "inorganic phosphate" in voluntary muscle, *Science*, 1927, *65:*401.
4. Myers, V. C. and Mangun, G. H. Comparative studies on creatine, phosphorus and potassium in various muscle tissues, *J. Biol. Chem.*, 1940, *132:*701.
5. Seecof, D. P., Linegar, C. R. and Myers, V. C. The difference in creatine concentration of left and right ventricular cardiac muscles, *Arch. Int. Med.*, 1934, *53:*574.
6. Cowan, D. W. The creatine content of the myocardium of normal and abnormal human hearts, *Am. Heart J.*, 1933-34, *9:*378.
7. Herrmann, G., Decherd, G. and Oliver, T. Creatine changes in heart muscle under various clinical conditions, *Am. Heart J.*, 1936, *12:*689.
8. Calhoun, J. A., Cullen, G. E., Clarke, G. and Harrison, T. R. Studies in congestive heart failure; the effect of overwork and other factors on the potassium content of the cardiac muscle, *J. Clin. Investigation*, 1930-31, *9:*393.
9. Mangun, G. H. and Myers, V. C. Normal creatine, phosphorus, and potassium content of human cardiac and voluntary muscle, *J. Biol. Chem.*, 1940, *135:*411
10. Alburn, H. E. and Myers, V. C. The creatine, phosphorus, and collagen content of different sections of the dog heart, *J. Biol. Chem.*, 1939, *131:*713
11. Wilkins, W. E. and Cullen, G. E. Electrolytes in human tissue; a comparison of normal hearts with hearts showing congestive heart failure, *J. Clin. Investigation*, 1933, *12:*1063.

12. Linegar, C. R., Frost, T. T. and Myers, V. C. Variation in creatine content of human cardiac and voluntary muscle at autopsy, *Arch. Int. Med.*, 1938, *61:*430.
13. Herrmann, G., Decherd, G., Schwab, E. H. and Erhard, P. Creatine content of digitalized normal and hypertrophied rabbit heart muscle, *Proc. Soc. Exper. Biol. & Med.*, 1936, *33:*522.
14. Myers, V. C. and Mangun, G. H. Some chemical observations on the human heart in health and disease, *J. Lab. and Clin. Med.*, 1940-41, *26:*199.
15. Mangun, G. H., Reichle, H. S. and Myers, V. C. Further studies on human cardiac and voluntary muscle; possible implications of changes in the creatine, phosphorus and potassium content, with special reference to heart disease, *Arch. Int. Med.*, 1941, *67:*320.
16. Burns, W. and Cruickshank, E. W. H. Changes in creatine, phosphagen and adenylpyrophosphate in relation to the gaseous metabolism of the heart, *J. Physiol.*, 1937-38, *91:*314.
17. Mangun, G. H. and Myers, V. C. Purine content of human cardiac and voluntary muscle, *J. Biol. Chem.*, 1940, *133:*lxii.
18. Herrmann, G. and Decherd, G. M., Jr. The chemical nature of heart failure, *Ann. Int. Med.*, 1938-39, *12:*1233.
19. Constabel, F. Über den Kreatingehalt des menschlichen Herzmuskels bei verschiedenen Krankheitszustanden, *Biochem. Ztschr.*, 1921, *122:*152.
20. Hastings, A. B., Blumgart, H. L., Lowry, O. H. and Gilligan, D. R. Chemical changes in the heart following experimental temporary coronary occlusion, *Tr. A. Am. Physicians*, 1939, *54:*237.
21. Blumgart, H. L., Gilligan, D. R. and Schlesinger, M. J. Degree of myocardial fibrosis in normal and pathological hearts as estimated chemically by collagen content, *Tr. A. Am. Physicians*, 1940, *55:*313.
22. Kalter, S. Ueber Glykokolbehandlung degenerativdystropischer Herzmuskelerkrankungen, *Deutsche med. Wchnschr.*, 1936, *62:*1371.

THE TREATMENT OF GOUT*

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INTRODUCTION

THE current trend in the management of patients afflicted with gout inclines toward acceptance of therapeutic principles that are physiologically sound or empirically satisfactory and rejection of those that fulfill neither criterion. Such a trend is encouraging in any malady and is particularly so in regard to gout because of the wide divergence of opinions which have been expressed in the past. There are several obstacles which have hindered progress in the evaluation of the treatment of gout and have delayed general acceptance of any regimen. In the first place, the etiology of gout is not known. The several theories are sufficiently dissimilar that treatment which may be directed toward correction of one causative mechanism may run counter to others which appear equally plausible to interested observers. Secondly, the pathogenesis of development of symptoms is inadequately understood. Evidence is not yet conclusive that gout is a disease primarily of articular or renal structures in contrast to a metabolic dyscrasia with joint and renal involvement as incidental processes. Thirdly, gout is a chronic disease and as in many chronic diseases there is great variation in the severity of somatic manifestations from patient to patient and considerable variation in the severity in afflicted persons during the natural course of the dyscrasia. Failure to appreciate this fact has led some physicians to attribute credit to a particular regimen, when in fact, the asymptomatic periods might have occurred irrespective of the treatment prescribed.

It is the conviction of the writer that there is no known cure for gout and that once the diagnosis is established the patient will have the malady throughout life. This does not mean that patients will have

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acute symptoms continuously if treatment be neglected. On the contrary, asymptomatic periods may persist for years in the absence of rigorous therapy. The malady, nevertheless, is a chronic disease as evidenced by (a) a persistent elevation of uric acid (urate) in blood and body fluids of all gouty patients, (b) failure of regression of bony changes once they have become visible by x-ray, and (c) progression of renal structural damage.

A liberal but not an inclusive interpretation of what is intended by the clinical term gout has been assumed in the preparation of this communication. Acute attacks of gouty arthritis, chronic deformed gouty joints, metabolic gout and gouty diathesis have been employed to express the various manifestations of the gouty dyscrasia. The first two phenomena are orthodox clinical realities and are recognized by most observers as such. Metabolic gout, i.e. a metabolic dysfunction responsible for the malady, persists throughout life in affected persons but the only suspicion of its presence between acute attacks of gouty arthritis is an increased concentration of serum urate and occasionally an increased excretion of urinary urate. The connotation, gouty diathesis, is mentioned frequently by various physicians although it is not universally accepted as a clinical entity. Several conditions, such as coronary sclerosis and gastrointestinal disturbances, have been attributed to the gouty diathesis in patients who show no evidence otherwise of suffering from acute gouty arthritis or metabolic gout. We are unwilling to subscribe to a catholic interpretation of the gouty diathesis and prefer to restrict its use in non-gouty persons to those members of gouty families who show an increased concentration of serum urate as discussed in the following paragraphs under heredity.

Heredity

It has been recognized for many years that the familial incidence of gout is high.[1] Recently it has been shown[2] that an increased concentration of serum urate in persons without gouty arthritis has a similar predominant familial incidence. Since 1935 more than 125 non-affected relatives of gouty patients have been investigated by us. The ages of the relatives varied from 6 to 86. Particular attention was given during the clinical questioning to the matter of joint symptoms in the past as well as to the clinical examination of joints for evidence of probable gouty arthritis. After a careful study it was concluded that none of the

supposedly non-affected members was suffering from gouty arthritis. The concentration of uric acid in the blood, however, was elevated in nearly 25 per cent of the total and was similar in magnitude to that observed in their kin who suffered from typical gout. In view of the early age at which some of the subjects were investigated, it seemed probable that the increased concentration of serum urate was present at birth or shortly after.

This phenomenon may be the true gouty diathesis. Of course it is also metabolic gout *sine* gouty arthritis. How many of the non-affected relatives will develop gouty arthritis subsequently will be most interesting. During the first six years after this study was started only one person with an elevated serum uric acid had an attack of gouty arthritis. It is possible that many will live a normal span of years without experiencing any attacks. Since gout manifests a strong male preponderance among afflicted persons, the tendency to gout is probably sex-linked and males rather than females should be watched for possible development of gouty arthritis. If the gouty diathesis is recognized in an otherwise healthy person, treatment should be similar to that recommended for intercritical gout with the exception that drugs are probably not indicated.

Acute Gouty Arthritis

The treatment of acute gouty arthritis should begin with the recognition of the prodromata of an impending attack. These include among other symptoms, polyuria, gastrointestinal unrest, suppression of sweating, and gain in body weight.[3] Many of the prodromata accompany a fall in barometric pressure[4] and at such a time the well informed patient will be particularly alert to the possibility of an impending attack. At the first appearance of premonitory symptoms, a few colchicine tablets (1/120 gr.) should be taken at hourly intervals. If the attack does not materialize within a few hours, further ingestion of colchicine is unnecessary. If symptoms progress from twinges and pangs to acute gouty pain, ingestion should be continued without interruption until an adequate amount of colchicine has been taken. The thought to be stressed at this point is the desirability of continual vigilance by the patient. It is probably no exaggeration to affirm that a few hours delay in beginning colchicine ingestion may determine the severity as well as the duration of acute episodes of gouty arthritis.[5]

A severe attack of gout may require from 8 to 16 colchicine tablets, the average is approximately 10, to achieve the desired effect. Adequacy is determined in the inexperienced by the appearance of untoward symptoms which include, nausea, diarrhea, and vomiting. Many patients learn from experience the optimum number of tablets to consume with each attack of acute gout and are able to obtain the desired alleviation of joint pain without the undesirable gastrointestinal symptoms. Until patients have acquired this information, it is imperative that the ingestion of colchicine be continued to the point of development of untoward symptoms before advising cessation. If a sufficient quantity of colchicine is taken, subsidence of joint pain usually begins after twelve hours and should be complete within a period of from twenty-four to forty-eight hours. A few acute attacks, less than 5 per cent in our experience, are not benefited materially by a single course of colchicine. If this be the case, a second course should be taken after a lapse of approximately three days. It is unwise to repeat the course earlier since gastrointestinal symptoms may develop before an amount of colchicine has been consumed adequate to affect joint symptoms.

General measures for the treatment of attacks of acute gouty arthritis include bed rest, an abundant fluid intake, a soft diet and sedatives. Bed rest usually is obligatory, nor is there any advantage to be gained by active motion of affected joints. A cradle for the bed clothes relieves local pressure upon involved structures. The application of hot or cold compresses contributes little since their soothing action is not great and alleviation of acute symptoms is not enhanced. An abundant intake of fluids is important and serves a dual purpose. During the acute stage of an attack there is an elevation of body temperature, increased sweating, and a decreased intake of water and salt from loss of appetite. Dehydration of the body may become pronounced and volume of urine output markedly reduced. With a restricted urine output there is an abnormally high concentration of urate in the renal tubules and precipitation of a portion of the urate as crystals. The damage to the kidney from this sequence of events may be one of the serious sequelae of an acute gouty attack. If the fluid intake is abundant, on the other hand, the internal environment of the body is maintained and volume of urine excreted is upheld. This can be achieved best by consumption of broths, soups, fruit juices and milk rather than by tea, coffee or sweetened beverages. The former fluids contain salts essential to the body which

are dissipated by sweating and need to be replaced in greater than normal amounts. A soft diet with a high percentage of carbohydrates is usually the choice of the sufferer. Aspirin, codeine, or morphine may be indicated to relieve pain. They usually are necessary for a period not exceeding twelve to twenty-four hours and should not be restricted if pain is severe.

Intercritical Periods

Acute attacks of gout should consume not more than a few days of each year; the great portion of the time then of any gouty patient is intercritical. Attention is centered as in the treatment of the acute attack upon physical activity, food, fluid and drugs. A gouty patient should be as active as possible between attacks. Prolonged bed rest after an acute attack has little beneficial effect upon gouty joints or upon the gouty dyscrasia and may be harmful in that it predisposes to an acute episode.

The diet recommended for gouty patients has been modified innumerable times through the centuries. The specific prohibitions have included carbohydrate, fat and protein. The conclusions of Ewart[6] written in 1896 are illustrative: "In gout, more than elsewhere, because of its idiosyncrasies, we should beware of *dogmatism*. Gout is undoubtedly prevented by starvation; yet it does not follow that it may be cured on that plan. Gout may also be prevented by strict avoidance of animal food. This does not prove that it need in every case be treated on vegetarian principles. Again, although gout may fail to attack some of those whose diet is exclusively animal, we are not warranted in prescribing meat as the diet for gout. Each case should be studied on its own merits." In the first edition of *The Principles and Practice of Medicine*, Osler[7] cautioned against the use of carbohydrate in gout as follows: "The conversion of azotized food is more complete with a minimum of carbohydrates than it is with an excess of them—in other words, one of the best means of avoiding the accumulation of lithic acid in the blood is to diminish the carbohydrates rather than the azotized foods. Meats of all kinds, except perhaps the coarser sorts, such as pork and veal and salted provisions, may be used. . . . Fats are easily digested and may be taken freely." The final statement is particularly interesting in view of the harm that has been attributed to fatty foods during the past decade.[8] It has been argued that if an excessively high

fat diet, 200 gm. or more, were capable of inducing an attack of gout, a low fat diet, 25 gm. or less, would be beneficial. While most physicians agree that an excessively high fat intake is not desirable, restrictions are not usually placed on a diet with an average fat content.

Foods high in content of purines, such as liver, kidneys and sweetbreads should be avoided at all times. The consumption of a liberal portion of other meats is probably harmless in the absence of advanced renal insufficiency. If a patient relates a close association between the ingestion of an article of diet and an acute attack, the advisability of avoiding this food is self-evident. Most gouty patients, however, are unable to detect any close association and in the absence of suggestive data, a diet balanced in content of carbohydrate, fat and protein is advised. This sentiment was expressed more than 200 years ago by Cheyne[9] as follows: "And indeed Temperance, and Moderation in everyThing necessary for the Support of Life is best and safest."

A liberal intake of fluids is important in the treatment of interval gout as it is during an acute attack. Spas and watering places of previous generations made a real contribution because of the custom of insisting upon copious imbibation of mineral waters. The qualitative mineral constituents were probably less important than the quantity of fluid consumed daily. The mechanism of the beneficial action of a large fluid exchange is clarified by the recent advances in understanding of renal processes, particularly in regard to the exchange of water and electrolytes.

It has been shown recently that the amount of glomerular filtrate formed by a normal person is more than 100 cc. per minute. It is a very constant amount under controlled conditions and is not altered appreciably by variations in fluid intake. Since glomerular filtrate is a protein-free filtrate of plasma, the amount of electrolytes including urate, present in the 100 cc. of plasma, is excreted through the glomerular membrane per minute. Of this amount at least 98 per cent of water and sodium chloride is reabsorbed by the renal tubules. If fluid intake is small, the per cent reabsorbed is even greater and less than 1 per cent of water may be received by the collecting tubules and excreted into the bladder. The reabsorption of urate, on the other hand, is quantitatively unlike that for sodium chloride and always is much less. Instead of a 98 per cent reabsorption of salt, as mentioned above, only 90 per cent of urate is reabsorbed, leaving 10 per cent available for excretion into

the urinary bladder.[10] If the solubility of urate were as great as the solubility of sodium chloride, the small amounts of water excreted would be sufficient to keep the large quantities of urate in solution. The solubility of urate in plasma and glomerular filtrate is near the maximum, however, and precipitation of urate and anatomical damage to the kidney are real possibilities. If a large amount of fluid is available for excretion because of a liberal fluid intake, precipitation of urate in renal tubules is inhibited.

The alcoholic content of fluids should be regulated by rules of temperance rather than abstinence. We have not observed any alcoholic beverage or group of beverages to be an offender in an appreciable number of gouty patients. A few patients sense the close association between drinking a particular beverage and onset of acute gouty arthritis. Avoidance of the particular beverage is recommended under such circumstances. Probably the most harm from consumption of alcohol is the quantity taken rather than the quality.

There are at least four types of drugs which have been used extensively in the treatment of gout. These are salicylates, cinchophen preparations, colchicine preparations and alkalis. Salicylates have a place in the modern scheme of gout thereapy if it is believed desirable to "purge" periodically the body of urate. In 1879 Sée[11] discovered that salicylates increased the urinary excretion of uric acid. Two years later Campbell[12] wrote a treatise on their use in gout and pointed out that while salicylates increased the urinary output of urate, colchicum has no effect upon urate excretion. Salicylates have been used intermittently and sporadically since then for their diuretic action as well as for their analgesic action.

Cinchophen has an effect upon urate excretion[13, 14] similar to that exerted by salicylate. There is no experimental data which suggests that either drug enhances urate output by altering the intermediary metabolism of purines.[15] Neither is there any appreciable increase in amount of urate filtered by the glomerulus nor any change in permeability of the glomerular membrane for passage of urate. The site of action most likely is in the renal tubules[16] and the process is one of inhibition of reabsorption of urate. The increased output in the urine is not unlike that which accompanies salyrgan diuresis[10] and is produced by a mild toxic action on the tubules and impedence of normal reabsorptive processes. Since cinchophen is known to be toxic to the liver cells, it is pos-

sible that it is mildly toxic for renal tubular epithelium as well.

Cinchophen is not used regularly at the Massachusetts General Hospital because it is not believed to be indispensable in the treatment of gout. The incidence of cinchophen intoxication and death from acute liver poisoning throughout many parts of the world is noteworthy. Furthermore, the analgesic action in acute attacks is less reliable than colchicine. We are solidly behind the attempt of the Food and Drug Administration to reduce to a minimum the ingestion of cinchophen in this country. Neocinchophen is reputed to be less toxic than cinchophen. Its action on renal exchange of urate is less powerful and if a similar quantitative effect upon this mechanism is desired, proportionately larger amounts of neocinchophen are needed. The supposed advantage of neocinchophen over cinchophen seems questionable.

Colchicine is believed by us to be indispensable in the treatment of gout. Patients with gout should never allow themselves to be without a vial of colchicine, whether at home, at work or abroad. The use of hermodatyl, the botanical from which colchicum is derived, is credited to Alexander of Tralles who recommended it to gouty patients in the 6th Century A.D.[17] In the 13th century Gilbert[18] recognized the Alexandrian discovery and referred to the colchicum preparation in use at that time as "Cathopcie Alexanderine." Benjamin Franklin, a sufferer from gout, is supposed to have introduced colchicum into the United States following his sojourn in France.[19] In 1820 Pelletier and Caventou[20] isolated the alkaloid colchicine from the meadow saffron or Colchicum autumnale. In the same year Haden[21] discoursed at great length upon the merits of colchicum and mentioned, among other things, the benefit derived from its use in a case of inflammatory fever in a horse.

Colchicine, the active ingredient of colchicum and the substance to be preferred in the treatment of gout, has gained considerable fame in recent years because of its action upon mitosis in plants. To produce this effect it is necessary to give, per unit mass of experimental material, approximately 100 times the therapeutic dose recommended for gouty patients. Suffice it to say, we do not need to concern ourselves about inducing cancer by the oral use of colchicine in therapeutic amounts, since the gastrointestinal tract rebels if this limit is exceeded by even a few tablets.

The pharmacologic action of colchicine in gouty patients is not known. In 1854 Gairdner[22] maintained that its beneficial action was not

related to an increased excretion of urinary urate. Recent studies in our laboratory have confirmed this.[10] In acute gouty arthritis it is almost specific for alleviation of pain. It is ineffective in non-gouty types of acute arthritis. The action of colchicine in intercritical periods is less specific than during acute attacks but, nevertheless, is beneficial to most patients. The majority of those afflicted should take some colchicine from time to time.[23] Those who experience not more than one attack a year will need a few colchicine tablets (1/120 gr. each) only at times when mild aches and pains in the joints appear. All other patients should consume some colchicine regularly. This habit may vary from not more than one or two tablets a week to a daily ration of one or more. Patients who have several attacks of acute gouty arthritis each year before beginning treatment should take at least two tablets on each of three days a week. In a few instances of severe gouty arthritis we have recommended two or three pills each day of the year. Several patients have followed this schedule for as long as five years and no untoward effects from the prolonged ingestion have been noted. Tolerance to the drug does not develop and if an acute attack supervenes, a full course of colchicine seems as effective as in patients who take the drug less frequently.

Alkaline waters and alkaline powders have some merit in the treatment of intercritical gout. The desirability of a large fluid exchange has been described. Alkaline powders have been advised because of the effect upon the hydrogen ion concentration of the urine. Urate is more soluble in an alkaline solution than in an acid media, the usual reaction of tubular urine. The increased excretion of urate in an alkaline urine, however, is quantitatively less than the increase which follows a large fluid exchange.

Chronic Deforming Gouty Arthritis

Low grade symptoms between attacks may persist in the joints of gouty patients with advanced structural changes. The symptoms are thought to be related to irreparable damage in the articular regions rather than to mild incipient acute attacks. Salicylates and colchicine are useful in control of such symptoms. Exercise is to be encouraged if the joints will permit it. Heat and massage are of little value.

The surgical treatment of chronically deformed gouty joints has not been explored extensively and until recently we have been reluctant to operate upon gouty joints. During the past five years, however, this

reluctance has been overcome chiefly because of the skilful management of the patients by R. R. Linton of the Surgical Service of the Massachusetts General Hospital. More than fifty operations have been performed upon gouty structures in more than twenty gouty patients during this interval. In some patients large tophi were removed from elbows, hands or feet. This was considered desirable because their size hindered normal movement of the limbs. In other patients, the urate tophi presented greater obstacles and the benefit was more pronounced by their removal. The patients were bedridden or semi-ambulatory from extensive deposition of urate in and about the articular structures of the feet. At least one tophus had broken down from trauma in each patient and a chronic sinus which discharged urate sludge persisted. Under such circumstances it was impossible to cleanse the sinus of bacteria before operation. In spite of almost certain contamination of the operative site extensive surgical procedures were consumated with no undesirable effects. Postoperative infection was never observed in any of the patients. None was treated before or after operation with any of the sulfonamide derivatives. The only specific drug given was colchicine. Three tablets were given daily for two or three days before the operation and for a similar period afterward. The incidence of postoperative acute gouty arthritis in patients prepared with colchicine was 8 per cent. In a control group of gouty patients not prepared with colchicine, the incidence of postoperative arthritis was 86 per cent. Of course the prophylactic use of colchicine at the time of any surgical procedure in a gouty patient is equally useful.

Summary

The modern treatment of gout as practiced by the writer is outlined in this communication. It is thought to be easy to follow and temperate in its prohibitions. The judicious ingestion of colchicine (1/120 gr. tablet) during the premonitory, incipient and inflorescent stages of acute gouty arthritis convinces the most skeptical of its merit. During the intercritical periods some colchicine, depending upon the severity of joint involvement, should be taken. The incidence of acute attacks may be markedly reduced by this regimen but unfortunately progression of chronic deforming changes is merely delayed and not prevented. An abundant fluid exchange aids in the elimination of urate and inhibits deposition of urate crystals in the renal tubules. A diet balanced in re-

gard to minerals, vitamins and foodstuffs should be consumed. If the periodic ingestion of a substance which augments urate excretion is desired, salicylate rather than cinchophen should be chosen. There remains but one discovery to be made, i.e., some substance which will inhibit the increased formation of urate in the body. When this has become a fact, metabolic gout will be a medical curiosity and urate tophi unique.

REFERENCES

1. Garrod, A. B. *A treatise on gout and rheumatic gout.* 3. ed. London, Longmans Green, 1876.
2. Talbott, J. H. Serum urate in relatives of gouty patients, *J. Clin. Investigation,* 1940, *19:*645.
3. Talbott, J. H., Jacobson, B. M. and Oberg, S. A. The electrolyte balance in acute gout, *J. Clin. Investigation,* 1935, *14:*411.
4. Talbott, J. H. and Coombs, F. S. Metabolic studies on patients with gout, *J. A. M. A.,* 1938, *110:*1977.
5. Talbott, H. Clinical gout, *Rocky Mountain M. J.,* 1941, *38:*186.
6. Ewart, W. *Gout and goutiness: and their treatment.* London, Baillière, Tindall & Cox, 1896.
7. Osler, W. *The principles and practice of medicine.* New York, Appleton, 1892.
8. Lockie, L. M. and Hubbard, R. S. Gout; changes in symptoms and purine metabolism produced by high fat diets in four gouty patients, *J. A. M. A.,* 1935, *104:*2072.
9. Cheyne, G. *An essay of the true nature and due method of treating the gout.* 7. ed. London, Strahan, 1725.
10. Coombs, F. S., Pecora, L. J., Thorogood, E., Consolazio, W. V. and Talbott, J. H. Renal function in patients with gout, *J Clin. Investigation,* 1940, *19:*525.
11. Sée, G. Études sur l'acide salicylique et les salicylates, *Bull. Acad. de méd.,* 1877, *6:*689.
12. Campbell, H. *The salicylic treatment of gout, rheumatic gout, neuralgia and diabetes.* 2. ed. London, Renshaw, 1879.
13. Nicolaier, A and Dohrn, M. Ueber die Wirkung von Cholincarbonsäure und ihrer Derivate auf die Ausscheidung der Harnsäure, *Deutsches Arch. f. klin. Med.,* 1908, *93:*331.
14. Weintraud, W. Die Behandlung der Gicht mit Phenylchinolincarbonsäure (Atophan) nebst Bemerkungen über die diätetische Therapie der Krankheit, *Therap. d. Gegenw.,* 1911, *13:*97.
15. Folin, O. and Lyman, H. On the influence of phenylquinolin carbonic acid (atophan) on the uric acid elimination, *J. Pharmacol. & Exper. Therap.,* 1912-13, *4:*539.
16. Hanzlik, P. J. *Actions and uses of the salicylates and cinchophen in medicine.* Baltimore, Williams & Wilkins, 1927.
17. Garrison, F. H. *An introduction to the history of medicine.* 4. ed. Philadelphia, Saunders, 1929.
18. Handerson, H. E. *Gilbertus Anglicus; medicine of the thirteenth century.* Cleveland, Cleveland Med. Lib. Association, 1918.
19. Schnitker, M. A. History of the treatment of gout, *Bull. Inst. Hist. Med.,* 1936, *4:*89.
20. Pelletier and Caventou. Examen chimique de plusiers végétaux de la famille des colchiceés et du principle actif qu'ils renferment, *Ann. chim. et phys.,* 1820, *14:*69.
21. Haden, C. T. *Practical observations on the Colchicum autumnale.* London, Burgess and Hill, 1820.
22. Gairdner, W. *On gout; its history, its causes and its cure.* 3. ed. London, Churchill, 1854.
23. Cohen, A. Gout, *Am. J. M. Sc.,* 1936, *192:*488.

TROPICAL MEDICINE IN UNITED STATES MILITARY HISTORY*

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THE subject of this paper has been chosen not so much to paint a picture of the past as to indicate what diseases among those ordinarily included in the field of tropical medicine are likely to be encountered by our military forces in the present conflict, and how some of them may be controlled. The advance in medical knowledge has been so great since the settlement of this country and particularly since the Spanish-American war, that the present narrative will show the practical disappearance of certain diseases from our armed forces; but our adventures into the tropics in the task we have now undertaken may well fill us with forebodings as to many of these diseases, and we may find ourselves confronted with others which we have heretofore not encountered.

In order to indicate what has and what has not been accomplished in the control of tropical diseases in United States military forces up to the present time, I shall outline briefly the history of the more important ones.

THE DIARRHEAL DISEASES

The diarrheal diseases include bacillary and amebic dysentery, cholera, salmonella and staphylococcus food poisoning, and the nonspecific diarrhea associated with the drinking of water polluted with sewage. Dysentery was one of the greatest handicaps to the permanent establishment of the Jamestown Colony which in essence was a military occupation. An epidemic of "bloody flux" assisted in the defeat of Braddock's campaign against the Indians in 1755. It undoubtedly was important in the War of Independence. During the War of 1812 it is said that on the frontiers in Vermont and New York State diarrhea and

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dysentery almost invariably overshadowed all other diseases and were the only ones which could be called camp diseases. The medical history of the War Between the States[1] devotes one of its two medical volumes entirely to the diarrheal diseases. The author of this volume, Joseph J. Woodward, was among the first to differentiate between the diphtheritic and ulcerative types of dysentery. He also recognized that it was often difficult to differentiate etiologically between dysentery and simple diarrhea. During that war there were recorded over 1,700,000 admissions for these diseases and over 44,000 deaths. They were the most important causes of illness in the Federal Army, and their case fatality rate increased progressively during the war, being six times as high in the last year as in the first. During the Spanish-American War the diarrheal diseases were reduced to about one-half their incidence in the War Between the States, but were second in rank only to malaria. During the World War they were under excellent control and had dropped to the seventh most important cause of illness. In France, however, there were several epidemics of bacillary dysentery in the A.E.F.,[2] and Emerson[3] reported that immediately after the Chateau Thierry operation probably as many as 70 per cent of the troops engaged suffered from diarrheal diseases. In the Philippines, even during the World War, these diseases caused by far the highest admission and death rate among the American forces.

Although the pathological picture of amebic dysentery had been differentiated from that of bacillary dysentery by Councilman and Lafleur[4] in 1891, and the pathogenicity of *E. histolytica* for man had been demonstrated in the Philippines by Walker and Sellards[5] in 1913, the first World War gave the chief impetus to the modern study of amebiasis, which has brought out the high incidence of *E. histolytica* in the general population and the importance of drinking water and flies in its transmission. In the latter connection, Craig[6] of the Army Medical Corps, described an epidemic of amebic dysentery among troops on the Mexican border in 1916, in which flies seem to have been the principal transmitting agent. We are still, however, not very far advanced in the control of amebiasis, since recent work indicates that the chlorination of water as prescribed for the killing of pathogenic bacteria will not kill the cysts of *E. histolytica*, although sand filtration, if properly conducted, appears to remove the cysts. This would probably be difficult in many situations in the present war. Craig's suggestion[7] of the

use of Diodoquin in weekly doses as a prophylactic may be of value for troops whose water supply may be polluted.

The importance of salmonella and staphylococcus diarrhea has been recognized only in recent years. During the first World War an epidemic of diarrhea was reported in a unit of the A.E.F. which found it necessary to eat bread which had been insufficiently cooked. This epidemic may well have been caused by staphylococcus toxin. In the present conflict where troops may have to advance rapidly in the field or jungle far from safe water supplies, the temptation will be for them to slake their tropical thirst with polluted water, which may incapacitate them with diarrhea, if not with typhoid or dysentery. It is to be hoped that our individual soldiers will be furnished with chlorine tablets for use in their canteens as one safeguard against these diseases.

Effective vaccines against the dysenteries have not been developed, so that the protection of military forces against them in the present war must be conducted by the strictest possible sanitary measures.

Cholera

Cholera was first introduced into this continent in 1832 and proceeded at once to cause a catastrophe in our armed forces, and to use them as a source of spread to the civilian population. Troops of General Winfield Scott proceeding to the Black Hawk War from New York by way of the Great Lakes, lost two thirds of their command from cholera and desertion.[8] Their progress was so delayed that they did not reach their destination until the war was over, but they did spread cholera down the Mississippi Valley. Again in 1867 cholera entered the United States and was spread by negro troops from Jefferson Barracks, Missouri, to other troops and civilians throughout Kansas and as far as New Mexico.[9] These were apparently the only two pandemics of cholera in which our armed forces were involved, and fortunately the modern knowledge of the disease has kept it out of North America and Western Europe during this century. There was a general outbreak of it, however, in the Philippines as late as 1934 and it is still endemic in India and China. A serious epidemic occurred in the coastal regions of China in 1938. Cholera vaccine, although not strongly antigenic, confers a certain degree of protection for a few months and the disease will possibly be prevented in our armed forces during the present war by repeated vaccination of those who may be exposed.

Typhoid Fever

Typhoid fever was not clearly described until 1829 and was not clearly differentiated from typhus until 1837, so that earlier records of its incidence are unreliable. During the War Between the States[10] over 75,000 cases and 27,000 deaths were ascribed to it. It stood next to diarrheal disease and malaria as a cause of illness and was second only to diarrheal disease as a cause of death. At that time Budd's demonstration[11] of the water transmission of typhoid fever had not been published, and although Woodward in discussing the etiology of the diarrheal diseases mentioned typhoid among the diseases which might be caused from "contagia" in the dejecta of the sick, he stated that the evidence was far from conclusive. The incidence of typhoid was highest in the first year of the war, the admission rate being 79 per thousand white troops. The rate decreased to 17 in the last year of the war but there was a steady increase in the case fatality rate from 25 per cent in the first year to 53 per cent in the last year. Whether this was due to exhaustion of the troops, to poorer care during more vigorous campaigns, or to inaccurate diagnosis is not indicated in the records. During the Spanish-American War typhoid fever was a major calamity. It took its chief toll among the volunteers, most of whom remained in the United States. Vaughan[12] gives the morbidity rate for typhoid as 193 cases per 1000, which means that nearly one-fifth of the troops contracted the disease. Deaths from typhoid constituted 86 per cent of the total deaths in the armed forces. The report of the investigating commission pointed out that the belief that typhoid was almost entirely transmitted by drinking water had led to the gross neglect of other sanitary methods of prevention. The lessons learned in this war, however, were invaluable for they indicated the necessity of rigid sanitation which thereafter became a major activity in the armed forces. Frederick Russell of the Army Medical Corps soon developed typhoid vaccine and in 1910 it was made compulsory for all personnel in the army.[13] The typhoid admission rate dropped practically to zero in 1913, and has remained at a very low figure since that time. Even during the first World War it was of negligible importance, as only 1529 cases were reported. Most of these occurred in France during the offensives which carried the troops into areas rapidly evacuated by the Germans. The control of typhoid was one of the greatest accomplishments in military

medical history. It is to be hoped that in the present conflict this disease may be of minor importance. Colonel Joseph F. Siler and his collaborators at the Army Medical School have recently made an important contribution to our knowledge of immunity following typhoid vaccination by the development of the mouse-protection test, and have made it seem probable that a frequent small stimulating dose of vaccine following the initial three doses, will confer a reasonable degree of immunity to the disease. It should be emphasized, however, that in the first World War sanitation was probably more important than vaccination in preventing infection, since most of the cases occurred in vaccinated individuals and our troops were not exposed to the total lack of sanitation existing in most parts of the tropics.

Malaria

Malaria probably always has been and still is the major endemic disease of most of the tropics inhabited by man. Recognized by the ancients, harassing the early settlers of this country, and taking its toll among civilians and soldiers alike until after the Spanish-American war, it has been deliberately controlled only in the most favored parts of the tropics and subtropics. During the War Between the States[10] it was the second most important cause of illness in the Federal Army and the third most important cause of death. Including typho-malarial fever, most of which was probably estivo-autumnal malaria, its death rate was 26 per 1000 white troops. The annual case rate increased progressively during the war. These were northern troops operating mostly in the southern states and the increase in rate undoubtedly indicates a progressively increasing reservoir of infection, which spread the disease in the northern states after the war. In the Spanish-American war[14] malaria was by far the most common disease. Its admission rate among volunteers, most of whom remained in this country, was 574 per thousand, and among Regular Army troops, many of whom went to Cuba and the Philippines, 695 per thousand. In other words, considerably over half of the troops had malaria.

In the occupation of Cuba following the Spanish-American War, Gorgas took measures not only against the yellow fever mosquito but against the Anopheles as well, and greatly reduced the death rate in Havana by drainage and other sanitary measures. When Gorgas transferred his activities to the Panama Canal Zone the malaria mortality was

reduced by similar measures but the disease has never been completely controlled because of the necessity of troop movements in unprotected areas.

We may expect a tremendous morbidity and mortality from malaria in the armed forces during the present conflict. Only by the most careful planning in advance can we hope to keep the incidence of the disease reasonably low, even in the predetermined bases established in the tropics. We have no true prophylactic against the disease. Quinine and atabrine when taken as prophylactic drugs merely postpone the development of symptoms in individuals bitten by infected mosquitoes. Already individuals connected with the defense program are returning from tropical areas suffering from the malignant estivo-autumnal disease. The relapse rate is high under the best known methods of treatment, and we may expect a large residue of chronic cases following the present war. Furthermore, the discovery that both quinine and atabrine decrease the efficiency of aviators at high altitudes, makes it inadvisable to use these drugs as preventives in these men, thus exposing the most important arm of the service to disability and ineffectiveness. There is indeed a great need for the discovery of a true prophylactic against malaria.

Yellow Fever

Yellow fever took its principal toll in this country before the War Between the States, although epidemics continued to occur as late as 1905. There is little evidence that it was important in our military history until the Spanish-American War. Then the campaign in Cuba and the subsequent occupation of the island made it an important military as well as civilian problem. There is no need to recount the brilliant work of the Army Research Board under Walter Reed in discovering the mosquito transmission of the disease, or Gorgas' successful campaign in eliminating it from Havana and the Canal Zone, or the practical elimination of it as an epidemic disease from Central and South America and the West Indies by the combined efforts of the Rockefeller Foundation and the Latin American countries. The brilliant work of the staff of the International Health Division of the Rockefeller Foundation in transmitting the disease to monkeys and mice, in determining its past and present distribution by the mouse-protection test and the viscerotome, in discovering its endemic existence in the

jungles of South America, and in developing an effective vaccine against it are also well known. Perhaps it is not so well known that the disease is endemic in Africa as far east as the Sudan, making the threat of its extension by rapid transport to the east coast of Africa and even to untouched Asia an ominous possibility. Although our armed forces will be protected by vaccination, they and commercial aviation may be the means of carrying it to virgin areas where *Aedes aegypti* can transmit it in its old epidemic form. No greater calamity to the people of Asia could result from the present war.

Other Tropical Diseases

Certain other diseases of the tropics which have not in the past been important in our military forces, should be mentioned because of their possible importance in the present conflict.

Bubonic plague is endemic in China, Burma, Indo-China, Java, India, Africa, South America and the western United States. In the United States it is slowly moving eastward toward the Mississippi Valley. Epidemics of pneumonic plague are always a threat in North China and small epidemics have occurred recently in Ecuador. Although a vaccine is available for military personnel going into endemic areas, it gives only partial protection, and the destruction of cities may well cause the occurrence of epidemics to which troops may be exposed.

Typhus fever has not been an important disease in our military forces since the War of Independence but it devastated Europe during the first World War and has often been a determining factor in military campaigns. It is to be hoped that effective louse control will prevent its becoming important in the present conflict. The endemic murine type of the disease transmitted to man by the rat flea has extended considerably in the southern United States during the past twenty years and the possibility that it may be the source of louse-borne epidemics should be kept in mind.

Leprosy, although not very infectious, caused a few individual tragedies among our troops in the Philippines following the Spanish-American war and a few cases may be expected in veterans of the present war. Since the disease is endemic in Louisiana, Texas and Florida, the exhaustion of our people by a long war might contribute to its further spread.

Beri-beri need be mentioned only because of its prevalence among

the Asiatics with whom our forces will be associated during the present war. It should be recalled, however, that its high incidence in the Philippines led Vedder of the Army Medical Corps to make it the subject of important studies with regard to its treatment and prevention, and led R. R. Williams into the study which recently accomplished the synthesis of thiamine.

Dengue fever, the transmission of which by *Aedes aegypti* mosquitoes was conclusively demonstrated in the Philippines by Siler and his co-workers of the Army Medical Corps, has a wide distribution throughout the tropics and subtropics and periodically causes devastating epidemics even in the southern United States. It is possible that the disease may incapacitate large bodies of our military personnel in the Far East at critical times during the present war.

Trypanosomiasis is a distinct threat to troops operating in the interior of Africa, and leishmaniasis or kala-azar is widely prevalent in the Mediterranean area, India and North China. Schistosomiasis, the blood-fluke disease, acquired by contact with water containing the larval stage, is endemic in Puerto Rico and other West Indian islands, in the northeastern countries of South America, in Africa, the Near East, Central China, Japan, Formosa and the Philippines, and precautions must be taken to keep troops out of infected water if possible. Already a report has been received that American soldiers may have become infected in a shower bath supplied from an infected pool. Finally, mention should be made of the highly fatal Far Eastern rickettsial disease, Japanese river fever, which is transmitted by a mite and is present in Malaya.

The Golden Age of Tropical Medicine in United States history was the first two decades of the present century, when yellow fever, malaria, hookworm, typhoid and the dysenteries were largely brought under control. Representatives of our Army and Navy Medical Corps and the U. S. Public Health Service were very important factors in this work, and the Bureau of Science in Manila gave experience to many men who have become our leading authorities on tropical medicine. Most of the men responsible for this Golden Age have now died or retired from active service, and relatively few young men have entered the field to take their places. It is to be hoped that one benefit which may accrue from the present world tragedy will be the stimulation of another group of young men to undertake the solution of the

many problems in tropical medicine which still remain. It is deplorable that, as in the Spanish-American war, we find it again necessary to send most of our young medical officers into the tropics with little or no knowledge of tropical diseases. This war will probably be a long one and it is not too late for the medical schools of the country to make tropical medicine as important a subject in the curriculum as it will be for medical graduates who accompany our armed forces to the tropics.

REFERENCES

1. Woodward, J. J. Medical history, in *The medical and surgical history of the War of the Rebellion,* Washington, U. S. Govt. Printing Office, 1879, pt. II, v. *1.*
2. Hall, M. W. and Michie, H. C. The diarrheal group of diseases in *The Medical Department of the United States Army in the World War,* Washington, U. S. Govt. Printing Office, 1928, v. *9,* chapt. 8.
3. Emerson, H. *Report of the Division of Sanitation and Inspection, Chief Surgeon's Office, A.E.F., May 31, 1919, to the Surgeon General, U. S. Army.* On file, Historical Division, Surgeon General's Office.
4. Councilman, W. T. and Lafleur, H. A. Amoebic dysentery, *Johns Hopkins Hosp. Rep.,* 1890-91, *2:*393.
5. Walker, E. L. and Sellards, A. W. Experimental entamœbic dysentery, *Philippine J. Sc.,* sect. B, 1913, *8:*253.
6. Craig, C. F. The occurrence of endamœbic dysentery in the troops serving in the El Paso District from July 1916 to December 1916. *Mil. Surgeon,* 1917, *40:*286; 423.
7. Craig, C. F. Medicinal prophylaxis of amebiasis, *Am. J. Trop. Med.,* 1940, *20:* 799.
8. Phalen, J. M. The cholera epidemic during the Black Hawk War, *Mil. Surgeon,* 1938, *83:*452.
9. Lull, G. F. Dissemination of cholera by the 38th Infantry in 1867, *Mil. Surgeon,* 1936, *79:*382.
10. Smart, C. Medical history, in *The medical and surgical history of the War of the Rebellion,* Washington, U. S. Govt. Printing Office, 1888, pt. III, v. *1.*
11. Budd, W. *Typhoid fever.* London, Longman, 1873; reprinted New York, George Grady Press, 1931.
12. Vaughan, V. C. *Epidemiology and public health.* 2v. St. Louis, C. V. Mosby, 1922.
13. Siler, J. F. and Lambie, J. S., Jr. Typhoid and paratyphoid fevers, in *The Medical Department of the United States Army in the World War,* Washington, U. S. Govt. Printing Office, 1928, v. *9,* chapt. 1.
14. Ashburn, P. M. *A history of the Medical Department of the United States Army.* New York, Houghton Mifflin, 1929.

EFFECT OF TONSILLECTOMY ON RESPIRATORY INFECTIONS IN CHILDREN*

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RESPIRATORY infections in infants and in children comprise the most common group of illnesses for that age group. Statistical evidence points to a lowered mortality and morbidity rate from these diseases during the last ten years but no specific measures have been developed that assure reasonably certain control of these common infections. Though the common respiratory infections termed colds, sore throat or tonsillitis, laryngitis, bronchitis and pneumonia represent the usual manifestations in infants and in children, such complaints as otitis media, cervical adenitis and sinusitis must be considered as a part of or as sequelae of respiratory infections.

Before assigning to respiratory infections any causative or influencing factors certain data pertaining to these infections must be recognized. Though children at all ages may contract any of the respiratory infections it has been demonstrated that all of these infections are most prevalent in the age grouping of three to seven years. It is also certain that geographical location and climatic advantages influence the occurrence of these complaints. These accepted facts must not be lost sight of when any single factor is considered that might influence the incidence or course of these respiratory infections in children.

Definite progress has been made in the control of respiratory infections. Advances in the science of nutrition, particularly with reference to vitamin and mineral needs have played a part in developing resistance to respiratory infections. Epidemiological studies leading to a more intelligent handling of children have aided in this control. To immunological studies and recently to chemotherapy can be ascribed significant gains in the management of these common infections. For at least two decades there has been a strong conviction among the medical profession and in lay groups that the tonsils and the adenoids play a significant

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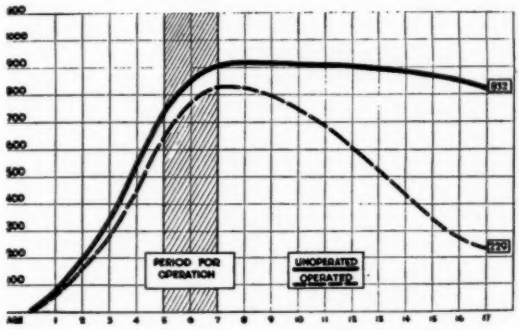

Chart 1. Tonsillitis and sore throat among 2,200 tonsillectomized and 2,200 nontonsillectomized children.

part in predisposing to or in prolonging these common infections in children. It is important therefore to study this supposed contributing factor to determine if possible the role of the tonsils and adenoids in respiratory infections.

Mindful of the fact that no scientific evidence is at hand to explain the part the tonsillar tissue plays in the economy of the child, it became necessary to follow the development of a group of children to adolescence, recording the sequence and the number of their respiratory infections over a period of years. It was possible to follow a group of 4,400 children for a period of ten years, half of whom had their tonsils and adenoids removed and the other half were not treated surgically. The initial examination and the observation of these children began when they were between the ages of four and seven years and continued into their high school period. At the time of their initial examination the indications for tonsillectomy were numerous but in general about the same for the entire group of children. For various reasons only one half of the total group (4,400) submitted to the operation, so the unoperated children served as controls. The incidence and the trend of a particular type of infection was noted in each child whether in the operated or in the unoperated group.

Tonsillitis: (Chart 1.) From these studies it was noted that tonsillitis was a common complaint in young children. Approximately 38 per cent of the 4,400 children utilized were subject to repeated attacks of tonsillitis (at least two febrile attacks a year) during the first seven years of life. As is indicated in Chart 1 the incidence of sore throat was de-

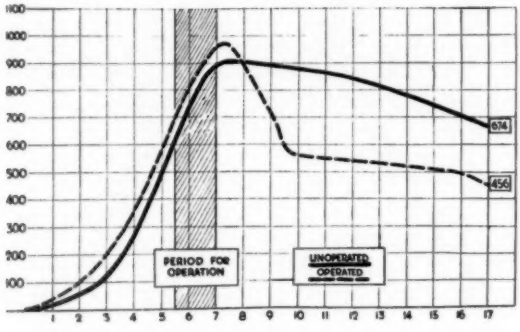

Chart 2. Colds (four or more a year) among 2,200 tonsillectomized and 2,200 non-tonsillectomized children.

cidedly lessened during the ten year period. In the group in which the operation was not done attacks of tonsillitis recurred with only a slight decrease in frequency during the same years. When one compares the incidence of this infection in the two groups it is obvious that the common ailment termed tonsillitis or sore throat occurred less frequently in the patients in whom the tonsils had been removed. In other studies, notably those of Selkirk and Mitchell,[1] similar results were obtained insofar as this complaint was concerned.

Common Cold: (Chart 2.) The common cold (four colds or more a year) occurred with about equal frequency in the two groups under observation. Approximately 42 per cent of the children were subject to this repeated infection up to the age of seven years. Over the ten year period the children who were operated on showed only a slight advantage over the children who were not, an advantage which cannot be considered statistically significant. It is quite likely that the removal of the adenoids benefited the younger children but as the children advanced in years the adenoid tissue retrograded, so that the children who were not operated on were likewise benefited. Though the trend, as far as frequent colds are concerned, is downward as the child increases in age, there is insufficient evidence to show that the role of the tonsils is a significant one, either in predisposing to or preventing this common infection. Adenoids, especially if they are obstructive, do play a significant part in predisposing to colds in young children but less so in older children.

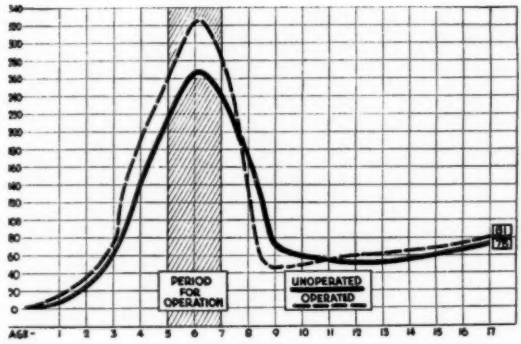

Chart 3. Otitis media (purulent) among 2,200 tonsillectomized and 2,200 nontonsillectomized children.

Otitis Media: (Chart 3.) Otitis media may exist independent of a respiratory infection but in many instances it occurs coincident with or as a sequela of other oral infections. Only purulent otitis media was considered in a study of this infection. It was noted that 15 per cent of the children who were subsequently operated on had suffered from purulent otitis media before the ages of from five to seven years, while in the control group 12 per cent were likewise affected. During the three year period following the tonsil and adenoid operation the incidence of otitis media was considerably lower in the operated group than in the unoperated children. It seems likely that the removal of the adenoids was responsible for this advantage, for during the next seven years the unoperated children fared as well and even a little better than those who were operated on. The age factor must be considered in evaluating the role of the tonsils and adenoids in this infection for, regardless of the presence or absence of the tonsils, this type of infection becomes less frequent after the eighth year of life. From these observations one can conclude that the tonsils play an insignificant role in the production of otitis media but that the adenoids may influence the incidence of this infection in children between three and eight years of age.

Cervical Adenitis: (Chart 4.) Cervical adenitis in children is usually secondary to a nasopharyngeal infection. It was noted that in each group, operated and control, 15 per cent of the children had definite enlargement of the cervical glands before the ages of five to seven years. Only

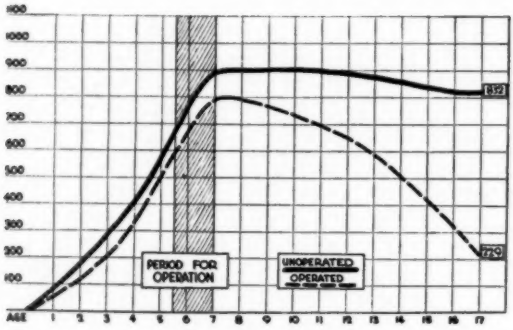

Chart 4. Cervical adenitis (acute and chronic) among 2,200 tonsillectomized and 2,200 nontonsillectomized children.

children in whom there was a visible enlargement of the cervical glands have been considered. During the three year period following tonsillectomy the incidence of cervical adenitis in the children who were operated on was 5 per cent as compared to an incidence of 14 per cent in the children who were not. Over a longer period of time a number of tonsillectomized children showed a recurrence of cervical adenitis, accounting for an incidence of 7 per cent at the end of ten years; while, among the children used as controls, the incidence of this complaint was 14 per cent. The statistical evidence in this study as well as in other reported studies shows a significant favorable trend for the relief of this complaint in the groups in which a tonsillectomy had been done.

Sinusitis and Nasal Allergy: Children with acute sinusitis, nasal allergy and allergic involvement of the sinuses are not favorably influenced by tonsillectomy. These conditions develop with equal frequency in children whose tonsils and adenoids have been removed in early childhood and in untreated children. The surgical removal of the tonsils and adenoids rarely benefits this condition. Observations made by Bullen[2] and recently by Hansel and Chang[3] indicate that the role of the tonsils and adenoids is not an important one in the causation and treatment of these manifestations.

Laryngitis: Recurrent laryngitis occurred in 3 per cent of the children before the operation and in 5 per cent of the children in the control group over the same period of time. For the three year period following tonsillectomy the incidence was not changed in either group.

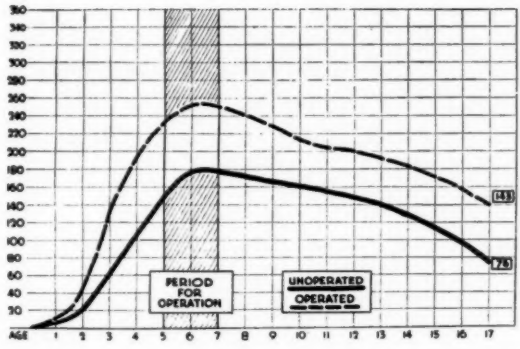

Chart 5. Pulmonary infections (bronchitis and pneumonia) among 2,200 tonsillectomized and 2,200 nontonsillectomized children.

At the end of the ten year follow-up period, 8 per cent of the children operated on were subject to recurrent attacks of laryngitis, while 10 per cent of the children used as controls were similarly affected. There is no obvious change in the incidence of this infection after the removal of the tonsils and adenoids and it would seem that the role of the tonsils and adenoids is not an important one in the occurrence of this infection.

Bronchitis and Pneumonia: (Chart 5.) In the case of upper respiratory infections the tonsils and adenoids are usually involved if they are present. In pulmonary infections these lymphoid structures may or may not be involved depending upon whether the pulmonary infection is primary or secondary to an upper respiratory infection. It is of interest, however, to discover, if possible, whether bronchitis and pneumonia occur less frequently or more frequently after the tonsils and adenoids have been removed. In analyzing the two groups it was found that pulmonary infections occurred more frequently in children during the first five years of life than in the next ten years. Such is the usual incidence of these infections. Undoubtedly some children subject to pulmonary infections are operated on because of this tendency, for more of the children who underwent the operation had repeated attacks of bronchitis and pneumonia before the ages of five and seven years than in the group of children who were never operated on. In spite of this, the trend was definitely for more pulmonary infections in the tonsillec-

tomized group over the ten year period than for the control children.

It seems that the absence of the tonsils either increased the chances of developing bronchitis and pneumonia or else the tonsillectomized group represented the more susceptible individuals and the operation was not responsible for the increased incidence of pulmonary infection. There seems to be no evidence to show that the tonsils and adenoids predispose the child to a pulmonary infection. There is suggestive evidence that the absence of the tonsils may encourage pulmonary involvement due to the fact that the soil in which bacteria might develop has been removed in the oral cavity.

When one reviews the statistical data dealing with the various infections it is quite evident that one can only talk about trends rather than what happens in an individual case. From clinical experience it is well known that the tonsils and adenoids play a very significant role in predisposing to respiratory infections, but can one deduce from these isolated results that the role of the tonsils is the same in all children? If it were so, the trends brought out by these statistical studies would be much more favorable for the operated group than our analysis shows. It can be assumed, however, that a favorable trend for a given infection in either group denotes the role the presence or the absence of the tonsils plays in the incidence of that infection. With that interpretation of the results it is clear that the tonsils and adenoids do play a significant role in the incidence of the upper respiratory infections while in the case of pulmonary infections the presence of the tonsils does not increase the incidence of bronchitis and pneumonia.

Recent advances in the treatment of respiratory infections may alter our opinion as to the significance of the tonsils and adenoids in these infections. The improved dietary factors which are now assured a large percentage of the children and the general use of sera and effective drugs in the treatment of respiratory infections have brought about a favorable effect on the morbidity and the mortality in these infections. The incidence and severity of respiratory infections has been shown to be less in adequately fed children than in children with known deficiencies in diet. The use of anti-pneumococcus serum and such drugs as sulfapyridine and sulfathiazole have materially reduced the mortality of pneumonia in children. Consequently the role of the tonsils and adenoids appears to be less important than during the period when no specific remedies were available. The control of the respiratory infections can-

not be considered accomplished however unless measures are developed that assure some degree of protection against the infection. It is in the field of prevention that the tonsils and adenoids may play an important role. One can therefore interpret the findings in this study as of significance in reducing the incidence of upper respiratory infections even though their removal does not tend toward a lower incidence of pulmonary infections.

Discussion

After making due allowance for the various procedures that are known to influence the incidence and the treatment of respiratory infections in children, the evidence gathered from this study does indicate that there is a relationship between the tonsils and adenoids and respiratory infections. If one separates these manifestations into upper and lower respiratory infections it is clear that the tonsils and adenoids influence the upper type of respiratory infections and do not favorably influence the lower or pulmonary infections. It is probable that the presence of the tonsils may even act as a safeguard against pulmonary infection inasmuch as the unoperated children showed a slightly lower incidence of bronchitis and pneumonia. The measurable benefits of tonsillectomy and adenoidectomy to the children who have been subject to tonsillitis, colds, otitis media and cervical adenitis justify the operation in these children and make it a desirable procedure. The benefits however, though striking in the case of tonsillitis and cervical adenitis, are not great enough to advocate a prophylactic tonsillectomy in children with the idea of reducing the incidence of respiratory infections. The statistical evidence agrees with the general clinical experience that certain types of upper respiratory manifestations can be reduced if the tonsils and adenoids are removed but other manifestations may actually occur more frequently following the operation. The type of respiratory complaint to which the child is most susceptible must determine whether the tonsils or adenoids are likely to be a liability to the child. From clinical experience and from a study of the statistical evidence some idea is obtained as to the role of the tonsils and adenoids in the case of a specific complaint. Where the role of the tonsils and adenoids appears to be favorable to the production of clinical symptoms the surgical removal of the tonsils is advocated.

Conclusion

The tonsils are undoubtedly responsible for many upper respiratory infections especially in children subject to tonsillitis and to cervical adenitis and can be considered as playing an important role in these infections. Tonsillectomy is desirable in such children.

The adenoids appear to be a causative factor in some children who develop frequent colds and middle ear infections. In the age period of three to seven years the adenoid structures are particularly a menace to many children and their removal does assure some protection against similar recurrent attacks. Adenoidectomy is advised in such children either alone or along with a tonsillectomy.

For the relief and protection against sinusitis and nasal allergy no statistical evidence is available to justify any protection by either the removal of the tonsils or adenoids or both organs. In the production of these clinical manifestations the tonsils and adenoids seem not to play any significant part.

Evidence obtained in this study does not support the opinion that laryngitis, bronchitis and pneumonia can be reduced in incidence by removing the tonsils and adenoids. It appears that laryngeal, bronchial and pulmonary infections are not dependent upon the presence or absence of the tonsils and that these lymphoid structures do not play a significant role in lower respiratory diseases.

Improved hygienic and dietary measures along with successful specific therapy of pulmonary diseases have brought about a condition which justifies the statement that is now generally accepted that the role of the tonsils and adenoids in the average child is not as important today in the control of respiratory infections as was thought to be the case a decade or two ago.

REFERENCES

1. Selkirk, T. K. and Mitchell, A. G. Evaluation of the results of tonsillectomy and adenoidotomy, *Am. J. Dis. Child.*, 1931, *42*:9.
2. Bullen, S. S. Effect of tonsillectomy in allergic conditions, *J. Allergy*, 1930-31, *2*:310.
3. Hansel, F. K. and Chang, C. S. Relation of allergy and tonsillectomy in children, *Arch. Otolaryng.*, 1940, *31*:45.

RELATIONSHIP OF UPPER RESPIRATORY INFECTIONS TO CHRONIC ARTHRITIS*

RALPH HENDERSON BOOTS AND ROBERT L. MCCOLLOM

DESPITE the fact that otolaryngology has reached a high peak in New York City, there seems to be as much chronic arthritis here as thirty years ago. Whereas there was one Arthritis Clinic in New York in 1920, now there are twenty-five, and all of them filled with patients. No one has gone so far as to place the blame for this on the Nose and Throat Surgeon, but these facts have been used as an argument against the removal of foci of infection for the treatment of the various forms of rheumatism.

Cecil and Angevine,[1] in a study of two hundred cases of typical rheumatoid arthritis reported that chronic focal infection played a comparatively unimportant role, and probably rightly stressed the idea that physicians should exercise a more conservative attitude regarding the treatment of tonsils, teeth, and sinuses. Recent writings such as this and discussions among rheumatologists have led to a swing of the pendulum away from removal of such foci. Perhaps it will swing too far and to prevent this, a review of our present knowledge is desirable, for we still believe that in certain cases of chronic rheumatism there is a relationship to upper respiratory infection. Surgical treatment is to be advised in many such cases, and one can expect definite improvement in the patients.

The thought that there could be a connection between dental or tonsillar infection and certain chronic diseases in the rest of the body goes back many years. However, it was not until the beginning of this century with the advance of bacteriology that this connection was popularized and an attempt made to place it on a scientific basis. Frank Billings,[2] in 1911, made the medical profession generally conscious of focal infection in the teeth, tonsils, sinuses, ears, gall bladder, appendix, urinary tract, prostate and bronchiectatic cavities. According to him,

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the chief systemic diseases which resulted from such infections were chronic arthritis, nephritis, cardiovascular degeneration, chronic neuritis and myositis. Many papers soon appeared in the literature on this subject and it was not long before a patient with chronic arthritis was examined primarily with the viewpoint of what further focus could be removed or treated. This period seems to have lasted until about 1930, when better methods of differential diagnosis of the various arthritic diseases lent a more critical attitude to such foci. No longer is the patient viewed as having "chronic arthritis," but as to whether or not he has rheumatoid arthritis (a chronic infectious form), osteoarthritis (a degenerative form), gonorrheal arthritis, tuberculous arthritis, gout or some other definite type. Obviously some of these were not primarily the result of "foci of infection."

During the past thirteen years of our investigations in the Arthritis Clinic at the Presbyterian Hospital, we have had an opportunity to make certain observations concerning this problem, and have gained definite impressions which can be presented. We see an average of one hundred arthritis patients each week, and it has been possible to make an accurate diagnosis of the type of arthritis in all except a very few cases. The ear, nose and throat examinations have been made by one of the authors, who has worked directly in the clinic in order to have a closer contact between the otolaryngologist and the internist. This direct collaboration has proven much more satisfactory than referring the patients for routine examination and care to the nose and throat clinic. In a preliminary report from our clinic in 1938, McCollom[3] stressed the importance of an accurate diagnosis; that there are many types of arthritis that we are sure are not nose and throat problems. He had encountered three patients with gonorrheal arthritis in one year, who had had the tonsils removed in an attempt to clear up the arthritis, without waiting to establish the diagnosis of the arthritis involved.

It is necessary to discuss each type of arthritis separately in order to gain an understanding of any relationship. Certainly it should be emphasized that in each, statistical studies of improvement following removal of foci are of little value. One need only consider the difficulty of evaluating improvement in rheumatoid arthritis with vaccines, sulphur, gold, bee venom, etc. These are definite substances. How much more difficult it is to evaluate the effect of removal of so-called diseased tonsils, when frequently it is impossible to say whether or not they are

diseased! So, our conclusions are drawn not so much from statistical studies as from a better understanding of the disease processes of the type of arthritis considered.

Rheumatoid Arthritis
(Synonyms: Atrophic, Chronic Infectious Arthritis)

About two-thirds of all cases of chronic arthritis fall fairly equally into one of two groups—rheumatoid arthritis and osteoarthritis.

The first of these, rheumatoid arthritis, is thought to be an infectious disease, in contradistinction to osteoarthritis which is considered a degeneration or "old age" of joints. It rarely kills, so that we see these fairly young patients year after year, and every form of therapy is tried. They are subjected to all sorts of cures. This has been the type of arthritis above all others in which it has been considered justifiable to remove any focus of infection, especially dead teeth or tonsils.

The typical picture is that of a young adult, thin, with symmetrical spindle-shaped or fusiform swelling of joints. The patient frequently has low-grade fever, anemia, vasomotor changes, subcutaneous nodules and sometimes enlargement of liver and spleen. It is a systemic disease and not one simply of local involvement of the joints. It occurs three times as frequently in women as in men. It is a disease of temperate climate—the farther south one goes, the less the incidence of the disease, it being practically unknown in tropical or desert regions. The incidence corresponds closely to that of hemolytic streptococcal diseases. Sixty per cent of such cases have agglutinins for hemolytic streptococci in their blood sera and this finding is used for differential diagnosis—such agglutinins not being found in any other chronic disease. Most investigators have held that there may be a definite relationship between this disease and hemolytic streptococcal infection. This relationship, however, is not definite, as no bacteria can be recovered from the blood stream or the joints of these patients. Instances in which the disease is ushered in by infections of the upper respiratory tract occur so frequently that a causal relationship is suggested. In some there appears to be a definite association between an attack of tonsillitis and the onset of the disease, while in other cases the sinuses seem to be responsible.

In Tables I and II is an analysis of 180 cases of rheumatoid arthritis, with reference to upper respiratory infections. Table III shows the results of tonsillectomy in this group.

TABLE I

RELATIONSHIP BETWEEN UPPER RESPIRATORY INFECTIONS AND RHEUMATOID ARTHRITIS IN 180 CASES

Group		*Cases*	*Percentage*
A	History of Upper Respiratory Infections (frequent sore throats, colds, grippe or sinusitis; much more frequent than average)	92	51%
B	Average or Less Than Average Upper Respiratory Infections	88	49%

TABLE II

92 CASES OF RHEUMATOID ARTHRITIS WITH FREQUENT UPPER RESPIRATORY INFECTIONS (Group A, Table I)

	Cases
Rheumatoid Arthritis Cases—Onset Immediately Following Upper Respiratory Infections	37
Rheumatoid Arthritis Cases Accompanied by Sinus Infections	58
(a) Purulent Sinusitis*	30
(b) Non-Purulent Sinusitis	28

* In most cases with the treatment of the purulent sinusitis, there occurred an improvement of the rheumatoid arthritis.

TABLE III

RELATIONSHIP BETWEEN TONSILS AND RHEUMATOID ARTHRITIS IN 180 CASES

	Cases	*Percentage*
Apparently Improved by Tonsillectomy (Practically all of these belong to Group A, Table I)	25	14%
Not Improved by Tonsillectomy	47	26%
Tonsils Removed Before Onset of Rheumatoid Arthritis	38	21%
Tonsillectomy Not Advised	54	30%
Tonsillectomy Advised but Pending	16	9%

From these figures and our clinical impressions, we have concluded that: (1) In 20 per cent of the cases examined, the disease seemed to be ushered in by an upper respiratory infection. (2) Patients with rheumatoid arthritis accompanied by purulent sinusitis usually improved with adequate treatment of the sinus infection. Such purulent sinus infections were found in 17 per cent of our cases. (3) It also seemed to us that the rheumatoid arthritis increased greatly in activity with any intervening upper respiratory infection. (4) The relationship between upper respiratory infections and rheumatoid arthritis has not been shown to be specific, and any improvement which occurs following the removal of tonsils and treating of purulent sinuses may be indirect, as it has long been known that anything which improves the general health helps this disease. (5) In years past, the importance of nose and throat infections in this disease has been overemphasized, but the internist who entirely ignores the presence of such infections seems to us guilty of neglect. (6) Although it seemed that measurable improvement frequently followed removal of diseased tonsils, yet routine tonsillectomy would not seem to be indicated, as it did not cause improvement in any convincing number of cases.

Osteoarthritis

Osteoarthritis, or hypertrophic arthritis, the other common form of chronic arthritis, is probably a degenerative disease—beginning at the time of life when other degenerations occur, and is probably as much a part of old age as the graying of the hair. The patient is past forty years, male and female equally involved—usually no history of following an upper respiratory infection. The patient is usually well-nourished or obese and healthy-looking. The joints involved, except for the distal joints of the fingers, are the weight-bearing joints—hips, knees, and spine. These patients are greatly benefited by rest, weight reduction, physical therapy and spa therapy. Exposure to cold frequently aggravates their complaints, just as occurs with old fracture cases, and with these old people, it is frequently desirable to have them spend their winters in a warm climate.

Focal infection rarely plays any demonstrable role, and one should not expect any improvement in the symptoms from tonsillectomy or treatment of sinuses. The indications for such treatment in patients with osteoarthritis should be on other grounds than their arthritis.

Rheumatic Fever

Very few cases of the acute type of rheumatic fever come to an arthritis clinic. A moderate number of cases with sub-acute or chronic involvement of the joints are seen with or without cardiac damage. Like rheumatoid arthritis, rheumatic fever is a disease mainly of temperate climates and apparently associated with hemolytic streptococcal infection. Most attacks begin in the early spring, the season of most frequent respiratory infections. In over 50 per cent of the cases the attack is preceded by acute sore throat, tonsillitis or sinusitis. The acceptance of the hemolytic streptococcus as the direct etiological agent is not general, many observers holding that the prodromal hemolytic streptoccal infection of the throat merely permits entrance of the true causative agent, or in some other way activates the disease.

In regard to treatment of upper respiratory infections in these cases, we take the liberty of quoting Swift,[4] who has had much more opportunity to form an opinion: "Rheumatic fever follows tonsillitis so frequently that tonsillectomy seems indicated if these organs remain diseased; for they may be the site of production of sensitizing substances or areas of infection whence bacteria are discharged into the blood stream. Preceding operation on any focus of infection, tonsils, sinuses or teeth, the patient should be placed under the influence of antirheumatic drugs in an attempt to prevent possible relapses. But the removal of tonsils does not insure absence of recurrences of the disease, for patients may have other sources of sensitization or may incur reinfection with hemolytic streptococci.

"Finally, in our present state of knowledge, it appears that the best prophylactic measure is to keep the patient free from hemolytic streptococcal infection. This indication is more easily stated than consummated. But public health measures of the future must recognize this important factor in the prophylaxis of infectious heart disease."

We have been especially interested in a group which seems to be a chronic form of rheumatic fever and includes many cases of that type of rheumatoid arthritis known as secondary progressive polyarthritis. These were formerly considered as rheumatoid arthritis following rheumatic fever, but the more we have studied them, the more it has seemed possible they are merely cases of chronic rheumatic fever. Clinically, the joints have the typical appearance of rheumatoid arthritis,

i.e., symmetrical fusiform swellings. However, the blood sera of these cases do not agglutinate hemolytic streptococci and they uniformally exhibit a high antistreptolysin titer. We have looked upon these cases as adult rheumatic fever. Practically all of them give a history of frequent sore throats or sinus infections, and experience indicates that it is very important in this group to remove diseased tonsils and treat sinusitis.

Infective Arthritis

Tuberculosis of joints, gonorrheal arthritis, arthritis occurring with lymphogranuloma venereum, lues, typhoid fever, suppurative arthritis due to staphylococci and hemolytic streptococci obviously have no relation to upper respiratory infections. Arthritis due to meningococci may have its origin in an upper respiratory infection with that organism.

Gout

Most physicians usually think of the acute attack of gouty arthritis as following dietary or alcoholic indiscretion. This conception is only part of the picture. Acute gout is precipitated just as frequently in the gouty individual by any acute infection. It is often surprising to see a gouty patient develop an acute attack during the convalescence from pneumonia, after having been for days on a soft or liquid diet and no alcohol.

We personally have seen a number of acute attacks of gout precipitated by antrum infections and acute tonsillitis, and it would seem logical to treat these.

Fibrositis

Other than rheumatoid and osteoarthritis, fibrositis is one of the most common conditions encountered in our clinic, and it is probably much more frequently seen in private practice. It is an umbrellalike term, not clearly defined, which includes bursitis, myositis, neuritis, and most non-suppurative inflammations of the supportive fibrous tissues. Certainly at the present time the term "fibrositis" is too loosely used and too frequently applied to any unexplained skeletal pain. Some authors divide fibrositis as follows: (1) Primary fibrositis, with involvement of fibrous tissue independent and not a part of any other disease; (2) secondary fibrositis; fibrous tissue changes secondary to rheumatoid arthritis, specific infections, trauma, etc.

In this presentation, we are concerned only with primary fibrositis. Many cases of morning stiffness of muscles, torticollis, lumbago, painful shoulders, are included as fibrositis. The etiology and pathology of most of these has not been determined and there is a definite need for investigation to clarify this problem.

Many of these cases seem to be related to upper respiratory infections, although the relationship has been difficult to prove. Most physicians have encountered painful shoulders, torticollis, and muscle aching accompanying sore throats, sinus infections, and recurrent colds. Usually with this group, improvement of the fibrositis may be expected with successful treatment of the sinusitis or removal of the diseased tonsils.

Focal Infection Arthritis

Modern classifications of arthritis do not recognize this term, and it is presumed by us that such cases should be classified as "infective arthritis, etiology unknown." Whatever name is given to these, we definitely see a very small group of cases which might truly be called focal infection arthritis. These are usually monarticular, and when they occur, the removal of the focus causes a disappearance of the arthritis. A most striking example of this, although not related to upper respiratory infection, was a young patient whom we had observed for a long period for recurring hydrarthrosis of the knee. Each time this knee flared up, she exhibited tenderness over the appendix. After removal of the appendix, the knee became entirely well. The mechanism of these cases is not known. Such cases also occur related to purulent sinuses and tonsillitis, and the results of the removal of the foci are most striking. These true focal infection arthritis cases are *rare*.

Conclusions

1. *Routine* tonsillectomy is not indicated in any form of arthritis.
2. A diagnosis of the type of arthritis should be made, before considering any relationship to a respiratory or any other focus.
3. Certain types of arthritis, such as osteoarthritis, gonorrheal arthritis, tuberculous arthritis, etc., are definitely *not* related to upper respiratory infection.
4. In rheumatoid arthritis particularly, it is wise to remove tonsils which seem diseased and to treat sinus infections, not because of any

proven etiological relationship, but because anything which improves the health of these patients seems to help their arthritis.

5. The question of tonsillectomy or treatment of sinusitis in any given case still is largely one of clinical judgment of the physician. Decision regarding such treatment is better made by combined study by the internist and otolaryngologist.

6. The necessity of taking a very careful history of upper respiratory infections in these cases is stressed.

7. Early treatment of the sinuses and early removal of the tonsils is necessary, if one is to expect any benefit in the rheumatoid arthritis group.

8. The results in private practice are probably better than in the clinics, as they are usually seen earlier and possible foci are treated and eradicated at an earlier stage of the disease.

REFERENCES

1. Cecil, R. L. and Angevine, D. M. Clinical and experimental observations on focal infection, with analysis of 200 cases of rheumatoid arthritis, *Ann. Int. Med.*, 1938, *12*:577.
2. Billings, F. Chronic focal infections and their etiologic relations to arthritis and nephritis, *Arch. Int. Med.*, 1912, *9*:484.
3. McCollom, R. L. Tonsils and sinuses in rheumatoid arthritis, *Laryngoscope*, 1938, *48*:314
4. Swift, H. F. Rheumatic fever, in *Textbook of medicine* (R. L. Cecil). 5. ed. Philadelphia, Saunders, 1940, p. 517.

TONSILLECTOMY AND ACUTE NEPHRITIS*

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THERE is no doubt about the close relationship between streptococcus infection (chiefly of the upper respiratory tract) and the pathogenesis of acute nephritis. Clinical, bacteriological and immunological studies give evidence of Streptococcus hemolyticus invasion in over 90 per cent of the cases of acute glomerulonephritis. The Streptococcus hemolyticus may come in through any portal but in the great majority of cases it comes in through the upper respiratory tract and associated structures. For our purposes there is not much use in making accurate anatomical diagnoses, since all the structures involved are not only contiguous but continuous.

In contrast to rheumatic fever the type of infection in nephritis is quite different. Instead of a mild, evanescent sore throat, such as precedes the rheumatic attack, the child who gets nephritis has a deep infection, such as cervical adenitis, mastoiditis or peritonsillar abscess. It is not the uncomplicated case of scarlet fever or tonsillitis that develops nephritis. What brings many children with nephritis to the clinic or hospital is not the nephritis but the cervical adenitis or mastoiditis, and the nephritis is discovered on routine examination. Having established a relationship between hemolytic streptococcus invasion of the upper respiratory tract and nephritis the question arises as to what can be done about it and, in particular, what is the effect of tonsillectomy.

Prophylaxis: There is no evidence that tonsillectomy plays any important role in preventing acute nephritis. Illingworth in England reported that 20 per cent of a large series had had tonsillectomy some time before the onset of acute nephritis. In Boston, Wessellhoeft reported the same incidence of postscarlatinal nephritis in those children with and without tonsils. In our series at the Babies Hospital approximately one-third of the patients with acute glomerulonephritis have had their tonsils removed. I do not see why one could expect a prophy-

* Read November 19, 1941 before the Section of Otolaryngology.

lactic effect, since the children who are destined to have acute nephritis are subject to repeated attacks of upper respiratory infection, and tonsillectomy in this group of children does not seem to materially lessen the incidence of upper respiratory infection. A point in the prophylaxis of nephritis which may be brought out here is the management of the preceding infection. If this primary infection could be treated so as to prevent the recrudescence of infection in the second to third week, which may be a precipitating factor in nephritis, it is conceivable that some cases of nephritis might be prevented. Obviously tonsillectomy and adenoidectomy do not prevent the septic complications which accompany acute glomerulonephritis. All forms of treatment in scarlet fever are said to lessen complications. None of the data is convincing. Chemotherapy offers an opportunity for a carefully controlled study of this question.

Shall tonsils be removed in cases of acute glomerulonephritis? When shall the operation be done? What are the results? Presumably the object in tonsillectomy in these cases is to prevent the development of chronic nephritis by removing a focus of infection which may be causing persistent renal damage and lessening the incidence of upper respiratory infection which also may further damage the kidney. There is no basis in fact for this conclusion. If we knew which children would develop chronic nephritis, the question could be answered. It is quite true that in the majority of children the improvement and healing process in nephritis parallels closely the activity of the infectious process and that, with persistence or recurrence of infection, urinary changes of a definite degree persist and recur. But I have seen prompt healing of the nephritis in the presence of persistent infection and I have seen nephritis progress into the subacute and chronic stage without any clinical evidence of infection. All of the above things can happen regardless of the presence or absence of tonsils, or tonsillectomy in the acute stage.

When chronic nephritis has become established I have never been convinced that any attack on foci of infection has altered the established course of the disease. Our experience is in agreement with that in Baltimore—that tonsillectomy did not prevent infection or exacerbation of the nephritis and that other factors must operate for recovery or progression. "The end is determined by the beginning."

With these divergent opinions and without any rational basis for action, what then is a reasonable attitude for the clinician to take. He

has to meet this problem and make a decision. Even though we are ignorant of the etiology and pathogenesis of glomerulonephritis, there does appear to be a relationship in some individuals between upper respiratory infection and nephritis, and if any of the generally accepted indications for tonsillectomy are present in a case of either acute or chronic nephritis, perform the operation. Nephritis itself is not to be considered an indication for tonsillectomy and adenoidectomy. It is an elective operation and the time for operation had best be decided for each individual case, preferably when the symptoms and signs of the nephritis have subsided and the pharynx is not acutely inflamed. When this is done, severe reactions have not been encountered in my experience, but I must admit that the beneficial effects are not proven.

GALILEO*

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GALILEO GALILEI was born at Pisa on February 15, 1564 when the Italian Renaissance was at its greatest height. His father Vincenzo, was an able mathematician, and a skilful musician. Galileo was educated at the monastery of Vallombrosa, near Florence, where he studied Greek, Latin and logic. In 1581 he went to the University of Pisa to study medicine. He devoted several years to these studies, and then yielded to his greater interest in mathematics and physics.

* In commemoration of the three-hundredth anniversary of the death of Galileo held at The New York Academy of Medicine.

While watching a lamp swinging in the cathedral he observed that whatever the range of its excursions they were invariably equal in time. The experimental verification of this fact led him to the discovery of the isochronism of the pendulum. Galileo immediately applied the new principle to the timing of the human pulse.

In 1585 Galileo returned to Florence, and in 1586 published the first description of his invention of the hydrostatic balance. His name soon became known throughout Italy. From 1589 to 1591 he carried on a series of experiments to determine the first principles of dynamics. His demonstration made from the Leaning Tower, before the professors, the students, and the people of Pisa, that bodies of different weights fall with the same velocity, marks an epochal achievement in the history of experimental science. In 1592 he was called to the University of Padua where he held the chair of mathematics until 1610. There he attracted the attention of students and persons of distinction who came from every part of the world.

The men of the Renaissance had set out to explore the nature of man and the cosmos. Man then was disclosed through the study of anatomy, pathology, physiology, and biology. Vesalius had already revolutionized the study of anatomy; Paré had modernized surgery. The studies of Cesalpino and Fabrizio had solved many important physiological problems, and Fracastoro had launched the new doctrine of the infectious nature of certain diseases. At this time too the discovery of countries, of plants, of animals, and of human species, until then unknown, further extended the intellectual horizons of the Age. The universe appeared then infinitely larger and more vast than the human mind had been able to conceive it. The relationships of man with all living things, with the sky and the earth, with animals and plants, appeared very different from those which had been accepted until then, and which had placed man in the center of the universe. Nevertheless, the belief that the earth was the center of the cosmic system seemed, because of its dogmatic character, to be unassailable and impregnable. Copernicus' discovery, though wonderful in its grandeur, had upset neither the supporters of the Ptolemaic doctrine nor those who believed every contrary statement to be inadmissible and heretical. The Copernican doctrine, expounded in a book written in rather obscure terms, and aiming primarily at the reform of the calendar, had not yet roused the protests of the strict supporters of the dogmas. Galileo, who had

begun by destroying with experimental proofs the principle of Aristotelian mechanics, had collected all the facts justifying complete acceptance of the Copernican theory, and had sensed the importance of Kepler's demonstration in 1609 that planetary orbits are elliptical. This discovery ended the Aristotelian dogma, which held that no celestial movement was possible except in a circular pattern.

Galileo succeeded in 1609 in producing a telescope of three-fold magnifying power; later he improved it until it had a magnifying power of 32. His instruments, of which he manufactured hundreds, were soon in demand in every part of Europe. His astronomical observations made with the aid of his telescopes so perfectly substantiated the truth of the Copernican doctrine that in 1610 he publicly proclaimed his convictions in the book, *Sidereus Nuncius.*

Galileo's discovery of the phases of Venus and of the satellites of Jupiter gave added proof to his belief. To save the crumbling edifice of dogmatism, however, the Tribunal of the Holy Inquisition declared the doctrine that the sun and not the earth is the center of the universe, and that the earth moves in its own orbit, to be absurd and heretical.

In 1632, at the time when the scientific world was upset by Harvey's discovery and experimental proof of the circulation of the blood, Galileo published in Italian, that is in a language accessible to the common people, his *Dialogo dei due Massimi Sistemi del Mondo.* This was greeted with tumultuous applause in every part of Europe. The strength and clearness of scientific exposition were here happily combined with great elegance of style. But this remarkable book was in flagrant violation of the decree of the Holy Office, and the author was cited to Rome by the Inquisition. On June 22nd the Tribunal compelled the 70-year-old man to recant, sentencing him to incarceration at the pleasure of the Tribunal, and enjoining him by way of penance to recite once a week for three years the seven penitential psalms. The judges doubtless had the illusion that they had defeated every attempt at rebellion, and had saved dogma by means of a punitive decree.

In reality however, Galileo's demonstrations effected a great revolution in thought to which the discovery of the microscope gave added impetus. In 1610 Galileo had adapted telescope lenses to the magnification of extremely small objects and constructed an instrument for the examination of the organs of very small animals. In 1614 he spoke about it to several friends, and Détarde, a scientist who visited him at

Florence, stated that with the aid of this instrument he had seen flies that were as big as sheep, and had observed that they are covered with hair and provided with angular joints. To this instrument a Greek scientist, Demisciamo, member of the Accademia dei Lincei to which Galileo belonged, gave the name "microscope." About the same time Galileo constructed the first thermometer, an air-thermoscope consisting of a glass bulb containing air connected to a glass tube or small ball dipping into a colored liquid. These successes of Galileo were in large measure due to his skill in perfecting the instruments he employed. He was thus the inventor of an effective telescope and of the compound microscope.

Galileo's conception of a mechanical universe dominated by mathematical laws swiftly reacted on the biological sciences. His conception of the cosmos proved that mechanical principles rule alike in the movements of the heavens and in the changes on the earth, in the revolution of a planet's satellites and in the structures of the human body.

Galileo's work was, therefore, not only creative in the field of astronomy but affected all scientific thought from its foundation. Scientific thought turned definitely toward experimental research following his principle: "the right way to attain truth is to put experience before all discussions." Attacking dogmatism with the greatest courage, he affirmed: "it is foolish to seek the meaning of natural things in the writings of this or that author, rather than in the works of nature which are always alive and at work before our eyes, true and unchanging in all their manifestations."

Galileo spent the last years of his life in his villa at Arcetri, in the strict seclusion which was the prescribed condition of his comparative freedom. His mental activities, however, continued undiminished till the last day of his life. He published in 1636 his *Dialoghi delle Nuove Scienze* in which he summarized the results of his experiments. His last discovery—of the moon's diurnal and monthly digressions—was made in 1637. Then he became blind. His genius, however, was at work until the last moment. As a teacher, as a philosopher, as a thinker, he was still active when he died on January 8th, 1642.

Based on Castiglioni's *The Renaissance of Medicine in Italy*, published by the Johns Hopkins University Press, Baltimore, Md., 1934; and *A History of Medicine*, published by A. Knopf, New York, 1941.

RECENT ACCESSIONS TO THE LIBRARY

"Possession does not imply approval"

Anderson, M. E. *Heart diseases.*
Clinton, Ia., Allen Printing Co., 1941, 110 p.

Angyal, A. *Foundations for a science of personality.*
N. Y., Commonwealth Fund, 1941, 398 p.

Bailey, H. & Love, R. J. M. *A short practice of surgery.* 5. ed.
London, Lewis, 1941, 1015 p.

Bell, G. H. *Experimental physiology.* 2. ed.
Glasgow, Smith, 1940, 192 p.

Boas, E. P. *Treatment of the patient past fifty.*
Chic., Year Book Publishers, [1941], 324 p.

Bonnin, J. G. *A complete outline of fractures.*
London, Heinemann, 1941, 507 p.

Clark, K. C. *Positioning in radiography.* 2. ed.
London, Ilford, 1941, 520 p.

Clendening, L. *Source book of medical history.*
N. Y., Hoeber, [1942], 685 p.

Gillespie, R. D. *Psychological effects of war on citizen and soldier.*
N. Y., Norton, [1942], 251 p.

Grove, R. C. *Sinus.*
N. Y., Knopf, 1941, 165 p.

Hartwell, J. L. *Survey of compounds which have been tested for carcinogenic activity.*
[Wash.], U. S. Public Health Service, [1941], 371 p.

Harvey, W. F.; Dawson, (Mrs.) E. K. (Chandler) & Innes, J. R. M. *Debatable tumours in human and animal pathology.*
Edinburgh, Oliver, 1940, 124 p.

Hathaway, S. R. *Physiological psychology.*
N. Y., Appleton-Century, [1942], 335 p.

Hospital for the Ruptured and Crippled. *Scientific papers presented at the seventy-fifth anniversary of the founding of the Hospital.*
[N. Y., New York Society for Relief of the Ruptured and Crippled, 1941], 215 p.

Howe, H. A. & Bodian, D. *Neural mechanisms in poliomyelitis.*
N. Y., Commonwealth Fund, 1942, 234 p.

Hutton, (Mrs.) I. G. (Emslie). *Mental disorders in modern life.*
London, Heinemann, 1940, 204 p.

Illingworth, C. F. W. & Dick, B. M. *A textbook of surgical pathology.* 4. ed.
London, Churchill, 1941, 728 p.

Kanner, L. *In defense of mothers; how to bring up children in spite of the more zealous psychologists.*
N. Y., Dodd, 1941, 167 p.

Kauffmann, F. *Die Bakteriologie der Salmonella-Gruppe.*
Kopenhagen, Munksgaard, 1941, 393 p.

Kelly, J. F. & Dowell, D. A. *Roentgen treatment of infections.*
Chic., Year Book Publishers, [1942], 432 p.

Lasher, W. W. *Industrial surgery.* Enlarged 1. ed.
N. Y., Hoeber, [1942], 472 p.

Lima, L. de S. & Alayon, F. L. *Sobre a significação patologica das lesões incaracteristicas (maculares simples).*
São Paulo, Revista dos Tribunais, 1941, 301 p.

Mitchiner, P. H. & Cowell, E. M. *Medical organisation and surgical practice in air raids.* 2. ed.
Phil., Blakiston, [1941], 296 p.

Mullen, E. A. *Hand-book of treatment.* 4. ed.
Phil., Davis, 1942, 707 p.

Raney, R. B. & Shands, A. R. *A primer on the prevention of deformity in childhood.*
Elyria, O., National Society for Crippled Children, 1941, 188 p.

Robb, G. D. *Medicine and health in New Zealand.*
[Christchurch, Whitcombe], 1940, 146 p.

Robertson, W. E. & Robertson, H. F. *Diagnostic signs, reflexes and syndromes.* 2. ed.

Phil., Davis, 1942, 327 p.

Sauer, L. W. *From infancy through childhood.*
N. Y., Harper, [1942], 200 p.

Savage, (Sir) W. G. *Practical public health problems.*
London, Churchill, 1941, 198 p.

Schall, W. E. *X-rays: their origin, dosage, and practical application.* 5. ed.
Bristol, Wright, 1940, 252 p.

Smiley, D. F. & Gould, A. G. *Community hygiene.* 3. ed.
N. Y., Macmillan, 1941, 448 p.

Snapper, I. *Chinese lessons to western medicine.*
N. Y., Interscience Publishers, 1941, 380 p.

Starling, E. H. *Principles of human physiology.* 8. ed.
London, Churchill, 1941, 1247 p.

Stein, J. M. *Your heart.*
N. Y., Alliance Book Corp., 1941, 240 p.

Taylor, F. S. *The conquest of bacteria from salvarsan to sulphapyridine.*
N. Y., Philosophical Library, 1942, 175 p.

Textbook (A) of surgery by American authors, edited by F. Christopher. 3 ed.
Phil., Saunders, 1942, 1764 p.

Van Liere, E. J. *Anoxia; its effect on the body.*
Chic., Univ. of Chic. Press, [1942], 269 p.

Wertham, F. *Dark legend, a study in murder.*
N. Y., Duell, [1941], 270 p.

von Witzleben, H. D. *Methods of treatment of postencephalitic Parkinsonism.*
N. Y., Grune, 1942, 164 p.

Yater, W. M. *The fundamentals of internal medicine.* 1. ed. [3. rev.]
N. Y., Appleton-Century, [1942], 1021 p.